新規テトラヒドロイソキノリン骨格を有するMGAT2阻害物質の創薬研究

新規テトラヒドロイソキノリン骨格を有する MGAT2 阻害物質の創薬研究

毒島　剛

本学位論文は、下記の原著論文を基に作成され、東北大学大学院薬学研究科に提出されたものである。

(1) **Busujima, T.**; Tanaka, H.; Shirasaki, Y.; Munetomo, E.; Saito, M.; Kitano, K.; Minagawa, T.; Yoshida, K.; Osaki, N.; Sato, N. Identification of 2-[2-(4-*tert*-butylphenyl)ethyl]-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (29) as an orally available MGAT2 inhibitor.

Bioorg. Med. Chem. **2015**, *23*, 5922-5931.

(2) **Busujima, T.**; Tanaka, H.; Iwakiri, K.; Shirasaki, Y.; Munetomo, E.; Saito, M.; Masuko, A.; Kitano, K.; Io, F.; Kato, K.; Kamigaso, S.; Nozoe, A.; Sato, N. Identification of 2-[2-(4-*tert*-butylphenyl)ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide as an orally active MGAT2 inhibitor.

Chem. Pharm. Bull. **2016**, *64*, 228-238.

(3) **Busujima, T.** and Tanaka, H. An efficient and convenient synthesis of acyl CoA: monoacylglycerol acyltransferase 2 inhibitor, 2-[2-(4-*tert*-butylphenyl)ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide.

Heterocycles **2016**, *92*, 470-484.

略語表

本論文中、以下の略語を使用した。

APCI：atmospheric pressure chemical ionization

AUC：area under the curve

BA：bioavailability

9-BBN：9-borabicyclo[3.3.1]nonane

BMI：body-mass index

DAG：diacylglycerol

DGAT：diacylglycerol acyltransferase

DMAP：4-dimethylaminopyridine

DMF：*N*,*N*-dimethylformamide

DMSO：dimethyl sulfoxide

EDC：1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EI：electron ionization

ESI：electrospray ionization

FeSSIF：fed state simulated intestinal fluid

HOBt：1-hydroxybenzotriazole

HPLC：high performance liquid chromatography

HRMS：high resolution mass spectrum

HTS：high-throughput screening

Hz：hertz

IPE：diisopropyl ether

IR：infrared radiation

i.v.：intravenous

J：coupling constant

LC/MS：liquid chromatography/mass spectrometry

LC/MS/MS：liquid chromatography/mass spectrometry/mass spectrometry

LCMS-IT-TOF：LCMS-iontrap-time-of-flight

2-MAG：2- monoacylglycerol

MC：methylcellulose

MGAT：monoacylglycerol acyltransferase

mp：melting point

MS：mass spectrometry, microsomal stability

MTP：microsomal triglyceride transfer protein

NMR：nuclear magnetic resonance

NOE：nuclear Overhauser effect

OLTT：oral lipid tolerance test

PBS：phosphate buffered saline

$PdCl_2$(dppf)：dichloro[1,1‘-bis(diphenylphosphino)ferrocene]palladium (II)

PK：pharmacokinetics

p.o.：per os

TFA：trifluoroacetic acid

TFAA：trifluoroacetic anhydride

TG：triglyceride

THF：tetrahydrofuran

TMS：tetramethylsilane

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序論

近年、高脂肪な食事を過剰に摂取することによる肥満症患者の急増は、世界的に問題となっている。

世界肥満実態（the Global Burden of Disease Study, GBD）調査によると、肥満者を含めた過体重者の人口は 1980 年では 8 億 8500 万人であったのに対し、2013 年では 21 億人まで増加したと報告されている。その割合は 1980 年には男性が 29%、女性が 30%であったのに対し、2013 年にはそれぞれ 37%と 38%にまで増加している。また、世界の肥満者の数は約 6 億 7100 万人まで上り、米国や日本などの先進国に留まらず発展途上国においても増え続けている [1)]。一方、日本においては、厚生労働省の平成 26 年「国民健康・栄養調査」によると、肥満者（BMI≧25 kg/m^2）の割合はここ 10 年間で大きな変化はないものの、男性 28.7%、女性 21.3%であると報告されている [2)]。

過度の脂肪摂取による肥満は、脂肪細胞が肥大することによってインスリン抵抗性を引き起こし [3-4)] 2 型糖尿病のリスクを高める。また、肥満が高血圧を誘発することも知られており [5)]、さらには肥満症と合わせて高血圧、高血糖および高中性脂肪血症のうち 2 つ以上該当すると、心筋梗塞や狭心症発症率が 36 倍上昇する統計データが報告されている [6)]。このように肥満症は糖尿病や高血圧といった症状との関連性が深く、これらが原因で心疾患のリスクを高めることから、肥満症を是正することは糖尿病や心疾患予防に重要である。

脂肪吸収メカニズムと生体内における MGAT2 の役割

食事として摂取した脂肪（トリグリセリド、TG）は、小腸管腔内で分解した後、小腸上皮細胞に吸収され、小腸上皮細胞内で再合成されて血中へと移行する[7]（Figure 1）。

トリグリセリドは、小腸管腔内で膵リパーゼにより 2-モノアシルグリセロール（2-MAG）と遊離脂肪酸に分解された後、小腸上皮細胞に吸収される。吸収された 2-モノアシルグリセロールは、モノアシルグリセロール　アシルトランスフェラーゼ（MGAT）を介して fatty acyl-CoA と結合し、ジアシルグリセロール（DAG）に変換される。すなわち、MGAT は 2-モノアシルグリセロールと fatty acyl-CoA からジアシルグリセロールを合成する触媒として機能し、小腸内での TG 再合成に重要な役割を担っている[8]。生成したジアシルグリセロールはジアシルグリセロール　アシルトランスフェラーゼ（DGAT）によってトリグリセリドとなり、ミクロソームトリグリセリド輸送タンパク（MTP）によってカイロミクロンに取り込まれる[9]。生成したカイロミクロンが腸管リンパへと分泌され、血中（体内）へトリグリセリドが移行する。通常はこのメカニズムによってトリグリセリドは体内へ取り込まれ、エネルギーとして蓄えられているが、脂肪細胞などに過度に貯蔵されることによって肥満症を引き起こす[10]。従って、血中トリグリセリド量を適切に制御する化合物は肥満症の治療薬となりうる。

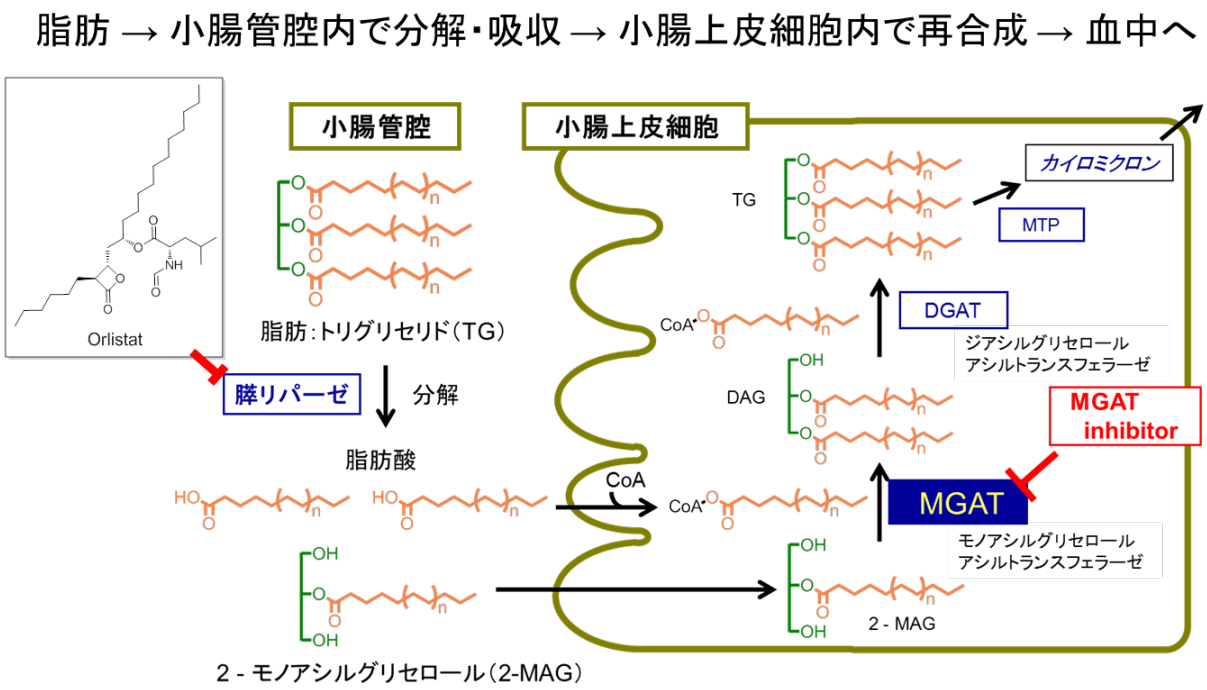


Figure 1. The proposed mechanism of triglyceride absorption and the structure of Orlistat.

摂取したトリグリセリドを分解する膵リパーゼの働きを阻害する薬剤として、オルリスタットが知られている（Figure 1）。オルリスタットは、リパーゼのセリン残基と共有結合することでリパーゼの作用を不活性化し、これによりトリグリセリドは 2-モノアシルグリセロールと遊離脂肪酸へ加水分解されない。トリグリセリドの分解が抑制されることで脂肪吸収を抑え有意な抗肥満作用を示すことが臨床試験により明らかとなっている。しかし、分解を受けなかったトリグリセリドがそのまま排泄されるため、脂肪便や便失禁という副作用を示す[11]。一方、小腸上皮細胞内に存在する MGAT、DGAT および MTP の働きを阻害することは、トリグリセリドの再合成および血中への移行を抑制することにつながることから、脂肪便などの副作用を示さずに脂肪吸収を抑制することが可能であると考えられる。しかしながら MTP、DGAT 阻害剤に関しては、それら薬剤の臨床試験の結果から有意な脂肪吸収抑制効果が認められるものの、副作用としてトランスアミラーゼの上昇といった肝機能障害や嘔吐・下痢といった消化管障害が報告されている[12-13]。

MGAT にはMGAT1、MGAT2 およびMGAT3 の3つのサブタイプが知られている[14-16]。ヒトにはこれら 3 つのサブタイプが認められているが、それに対してげっ歯類にはMGAT1 および MGAT2 が知られており MGAT3 は発現していない。MGAT1 は胃・腎臓、MGAT2 は主に小腸、MGAT3 は小腸のみに発現している。このことから、MGAT2 および MGAT3 が小腸での脂肪吸収に関与していると考えられている（Figure 2）。

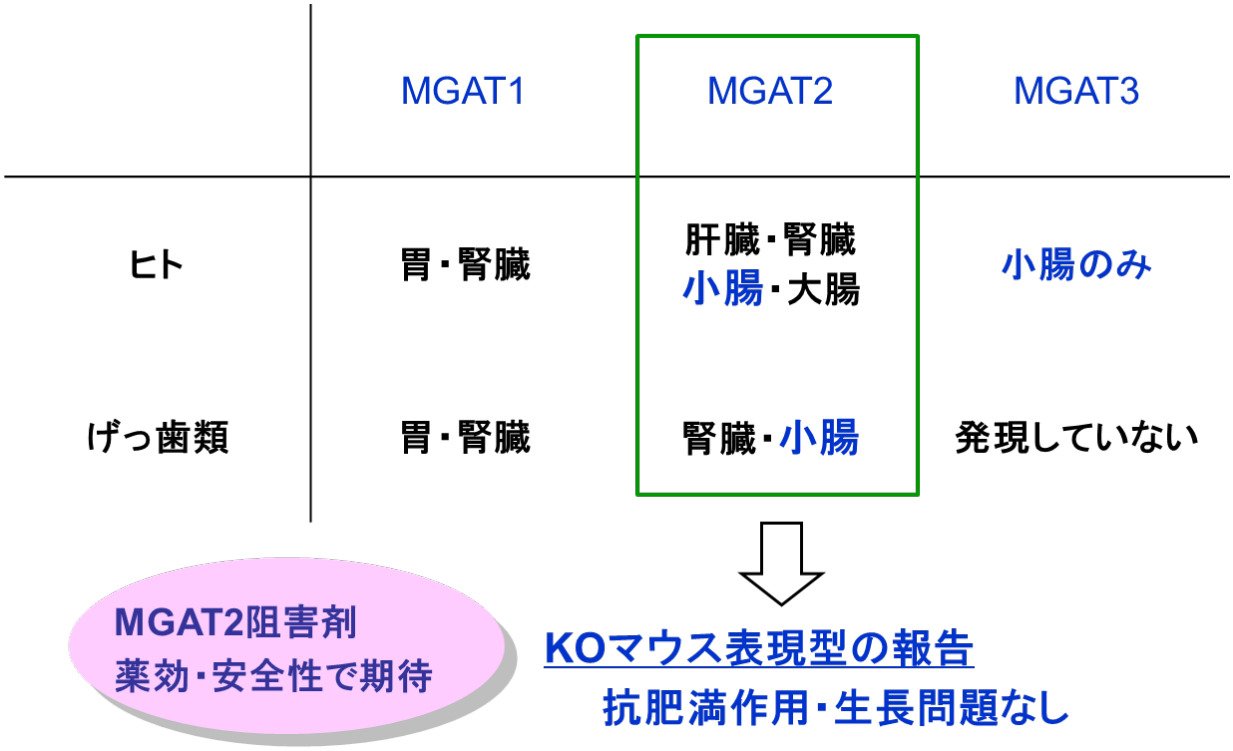


Figure 2. Three isoforms of MGAT enzyme.

MGAT3 はげっ歯類において発現していないため、その薬効および安全性に関する情報は得られていない。一方、MGAT2 ノックアウト（KO）マウスに関する情報が 2008 年に報告された[17]。MGAT2 KO マウスは生長に問題がなく、一般所見、病理解析においても異常が見られておらず、オルリスタットや DGAT 阻害剤、MTP 阻害剤などで見られた消化管症状や肝機能障害も観測されていない。MGAT2 KO マウスを用いた脂肪負荷試験において顕著な吸収抑制作用を示しており、これは MGAT2 が小腸での脂肪吸収に関与していることを示唆している。また、MGAT2 KO マウスに高脂肪食を負荷し

た場合に、野生型マウスと比較して体重および体脂肪量が有意に低下しており、血中コレステロールや血糖の低下も認められた。さらに MGAT2 KO マウスはエネルギー消費量が亢進することも明らかとなっており [18-19]、MGAT2 はエネルギー消費量を調節する機能を持つ酵素であると期待されている。

以上の事実から、生体内での脂肪吸収に関与している MGAT2 は、薬効面および安全性の面から魅力的なターゲットであると言える。そこで筆者は、経口活性を有する新規 MGAT2 阻害剤を開発することで、MGAT2 KO マウスで示された体脂肪量の減少が阻害剤でも同様に確認できるかどうかを明らかにし、MGAT2 が抗肥満薬として有望な標的分子であることを実証するため本研究を行った。

MGAT2 阻害薬の現況と本研究成果概要

MGAT2 阻害活性を示す低分子化合物が 2008 年に大日本住友製薬によって初めて報告された [20-21]（Figure 3）。その後、Merck-万有製薬 [22]、Bristol-Myers Squibb 社 [23-24]および Eli Lilly 社 [25]から相次いで報告され、これらの化合物はいずれも in vitro 酵素阻害試験において、IC_{50}値が nM オーダーの高い MGAT2 阻害活性を示している。しかしながら in vivo 薬効試験に関する情報は報告されていない。唯一、in vivo 薬効試験の報告がなされている AstraZeneca 社のスルホンアミド化合物は、in vitro の pIC_{50}値が 8.2 の MGAT2 阻害活性を示しているが、マウスを用いた脂肪負荷試験では 150 mg/kg という高用量においてのみ有意な脂肪吸収抑制効果を示す [26]。すなわち、近年 MGAT2 阻害剤の報告は増加しており [27-28]、各社とも創薬標的としての MGAT2 に対する関心の高さが伺えるが、動物レベルにおいて低用量から in vivo 薬効を示す強力な MGAT2 阻害剤の報告例はない。

そのような状況下で筆者は、経口投与可能で低用量から in vivo 薬効を示す新規 MGAT2 阻害物質の創出を目的に、大正製薬保有化合物ライブラリーを用いて High Throughput Screening (HTS)を実施した。

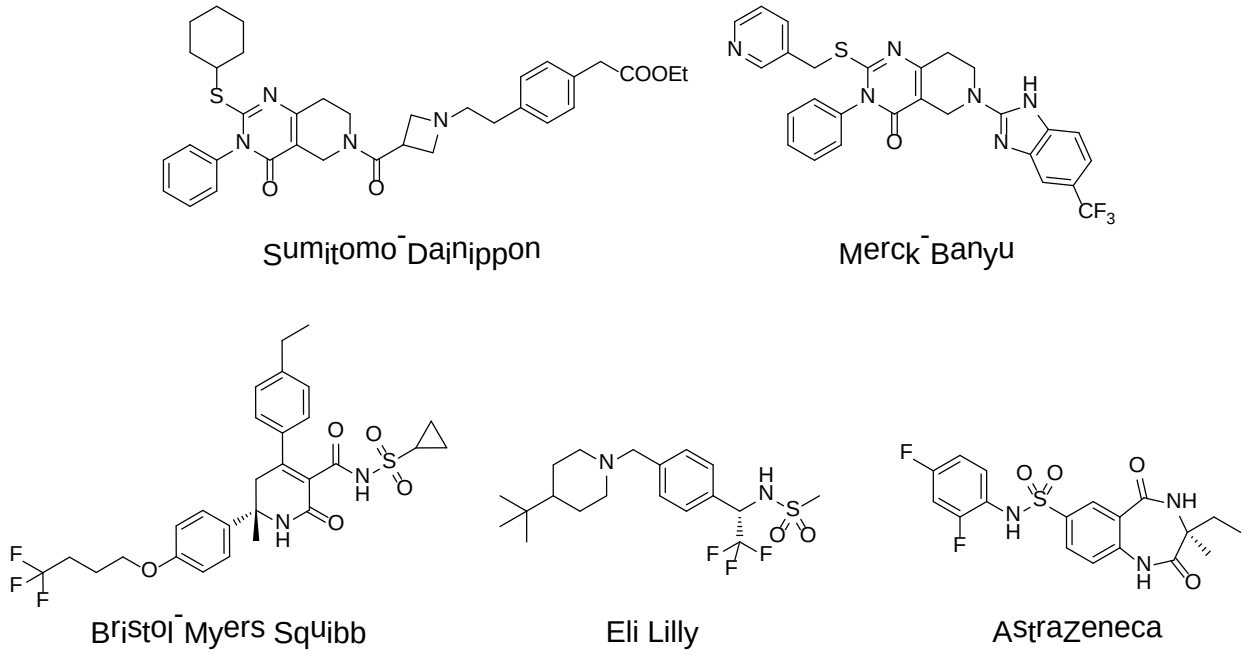


Figure 3. Chemical structures of reported MGAT2 inhibitors.

筆者は、大正製薬保有化合物の HTS によりヒット化合物 **1** を同定した（Figure 4）。化合物 **1** は HTS ヒット化合物として良好なヒト MGAT2 阻害活性（hMGAT2 IC_{50} = 594 nM）およびマウス MGAT2 阻害活性（mMGAT2 IC_{50} = 1310 nM）を有していたが、溶解度が極めて低い化合物であった（< 0.07 μg/mL in water）。そこで、酵素阻害活性の向上および溶解度の改善を目的に化合物 **1** の誘導化を行った。

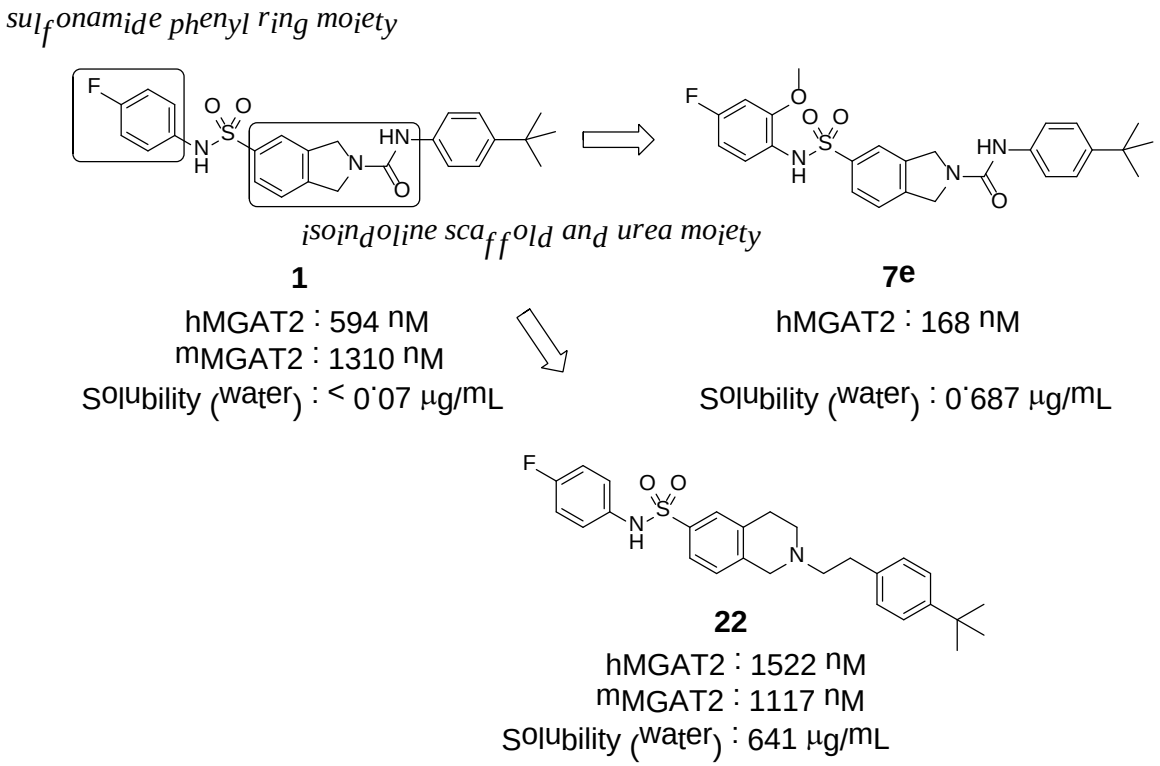


Figure 4. Modification of HTS hit compound **1** to **7e** and **22**.

本論第 1 章では、活性および溶解度の向上を目指し、化合物 **1** のスルホンアミド窒素に置換するベンゼン環のオルト位およびパラ位の置換基変換、そしてイソインドリン構造やリンカー部位の変換を行った。まず、スルホンアミド窒素に置換するベンゼン環の置換基変換を行ったところ、酵素阻害活性の向上したイソインドリン誘導体 **7e**（IC_{50} = 168 nM）を見出した。オルト位に置換基を導入した化合物 **7e** の溶解度は化合物 **1** と比べ向上したが（0.687 μg/mL in water）、マウスを用いた薬物動態（pharmacokinetics, PK）試験にて 100 mg/kg の用量で経口投与したところ血中曝露量は極めて低い結果であった（C_{max} = 94.3 ng/mL, $AUC_{0\text{-}4h}$ = 134 ng•h/mL）。次に、イソインドリン構造およびリンカー部位の変換を行ったところ、溶解度が化合物 **7e** より約 1000 倍向上した化合物 **22**（641 μg/mL in water）を創出した。この化合物 **22** は、マウス PK 試験において化合物 **7e** と比べて 10 倍以上血中曝露量が向上したため（C_{max} = 1200 ng/mL, $AUC_{0\text{-}4h}$ = 1808 ng•h/mL）、本化合物を用いてマウス in vivo 薬効試験を検討した。第 1 章ではこれら化合物の構造

活性相関並びに化合物 **22** の in vivo 薬理作用について述べる。

本論第 2 章では、第 1 章で得られたイソインドリン誘導体の構造活性相関の情報を活用した化合物 **22** の最適化検討について述べる。すなわち、スルホンアミド窒素に置換するベンゼン環のパラ位置換基を変換し、化合物 **22** よりも MAGT2 阻害活性が向上した化合物 **37**、**39** および **44c** を見出した（Figure 5）。これら化合物の溶解度測定や肝代謝安定性などの各種 in vitro 試験、またマウス血中曝露量測定や in vivo 薬効試験を実施した。その結果、3 mg/kg の用量から有意な脂肪吸収抑制作用を示す化合物 **39**（**TP0455353**）を同定した。第 2 章ではこれらの試験結果から、溶解度と血中曝露量、並びに脂肪吸収抑制効果の関係性について考察する。

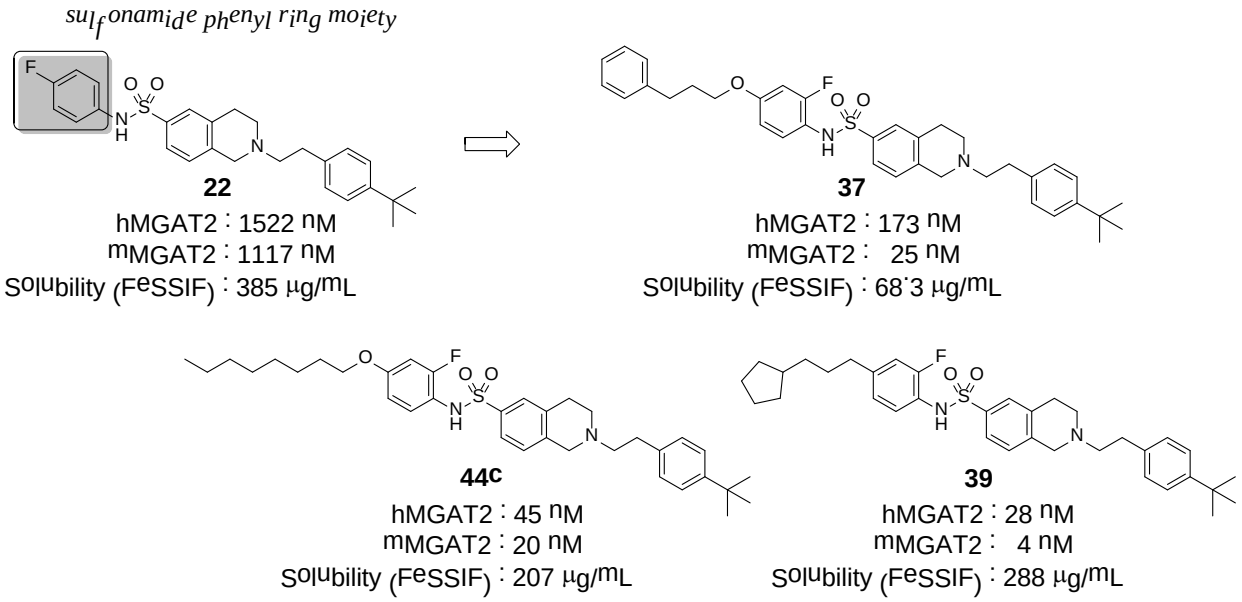


Figure 5. Optimization of compound **22** to representative compounds.

本論第 3 章では、第 2 章で見出した化合物 **39**（**TP0455353**）の効率的合成法について述べる。化合物 **39**（**TP0455353**）はマウス in vivo 薬効試験において 3 mg/kg の用量から脂肪吸収抑制効果を示し、抗肥満薬として期待される化合物である。今後、他の動物種での薬効試験や反復投与薬効試験などの高次薬理試験および安全性試験を行うにあ

たり、大量の化合物供給が必要となる。化合物 **39**（**TP0455353**）の初期合成法は、総収率が 6 工程で 6.8%と極めて低いものであった（Figure 6）。これは、テトラヒドロイソキノリン誘導体 **16** に対するクロロスルホニル化反応の位置選択性の低さおよびその位置異性体を分離するためにカラム精製が必須であるといった問題に起因している。

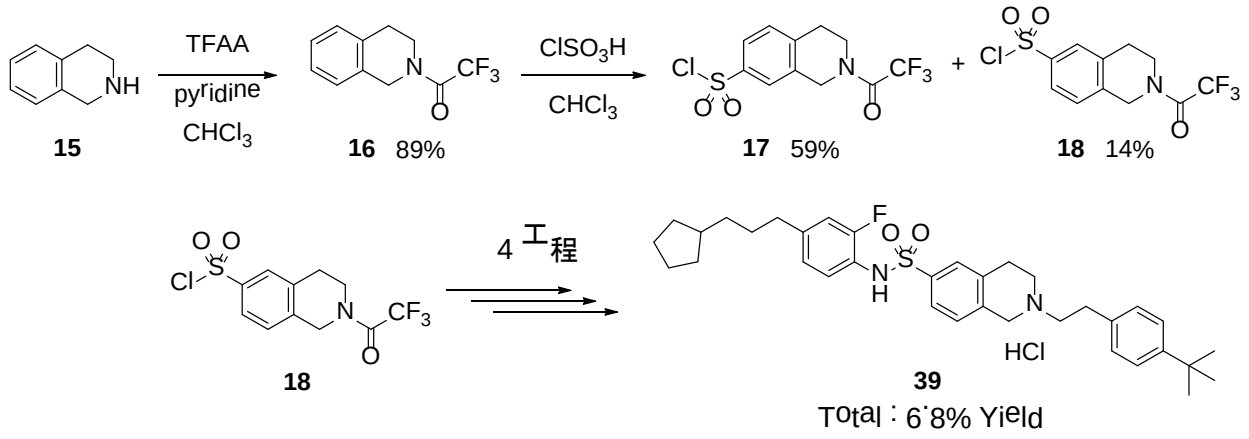


Figure 6. Primary synthetic route and 100 g scale synthesis of compound **39** (**TP0455353**).

筆者はテトラヒドロイソキノリン構造のベンゼン環の電子密度計算から、反応条件の制御では 6 位選択的にクロロスルホニル化反応を行うことは困難であると推察した。そこで、出発原料として 7 位にブロモ基が導入された化合物 **31** を用いた合成ルート検討を行った。その結果、各工程とも良好な収率で反応が進行し、効率的に 6 位クロロスルホニル体を合成できた。しかし、本合成ルートにおいて、出発原料に導入した 7 位のブロモ基を除去するために用いる Pd-C 触媒の使用量（基質に対して 50 wt%）を低減することが課題であった。種々検討した結果、トリエチルアミンを添加剤として用いた場合

に Pd-C の使用量の低減化に成功し、広い基質一般性をもって脱ブロモ化反応が進行することを明らかにした。第 3 章ではスケールアップ合成可能な新規合成ルートを確立し、100 g の化合物 **31** から 7 工程にて 84.5 g（総収率：45%）の化合物 **39**（**TP0455353**）を得ることに成功した検討結果について詳述する。

本論

第 1 章　経口投与可能な脂肪吸収抑制作用を有する新規テトラヒドロイソキノリン誘導体の創出

第 1 節　HTS ヒット化合物の課題と合成戦略

経口投与可能な新規 MGAT2 阻害物質の創出を目的に、大正製薬保有化合物ライブラリーを用いた HTS を実施した。得られたヒット化合物の酵素阻害活性およびその周辺化合物の構造活性相関、構造新規性や構造変換の多様性といった構造上の特性から、MGAT2 阻害活性（IC_{50}）が 594 nM であった化合物 **1** に着目した（Figure 7）。化合物 **1** は中程度の MGAT2 阻害活性を示したが、その溶解度は極めて低いものであった（< 0.07 μg/mL in water）。

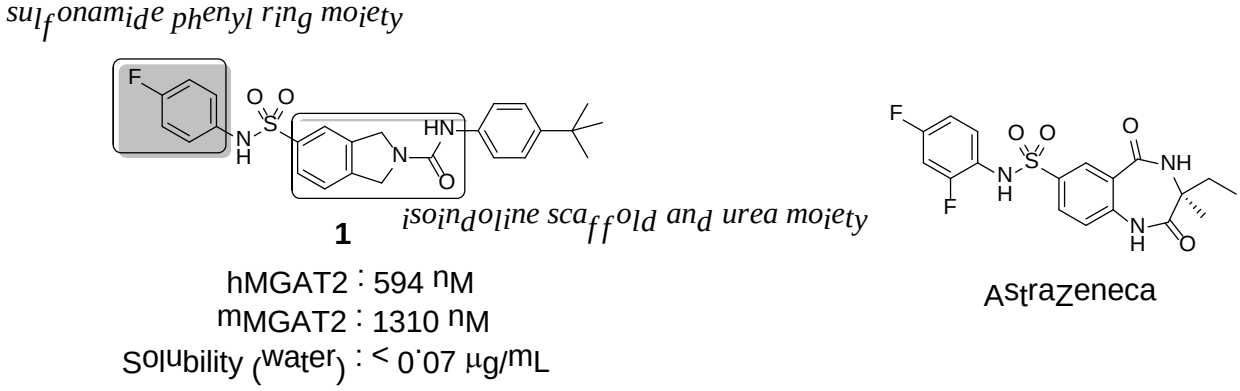


Figure 7. HTS hit compound **1** and other sulfonamide derivative as a MGAT2 inhibitor.

スルホンアミド構造を有する MGAT2 阻害剤として AstraZeneca 社の化合物が報告されているが [26]（Figure 7）、化合物 **1** はこれまで報告されていた他の MGAT2 阻害剤と比

較して新規なケミカルクラスの化合物であり、新たな MGAT2 阻害物質の創製につながるものと期待した。そこで筆者は、構造変換の戦略として MGAT2 の阻害活性を向上させ、かつ溶解度を改善することを目的に化合物デザインを行った。

一般に新規薬物のドラッグデザインは、X 線結晶構造解析などから得られた標的タンパクの 3 次元立体構造に基づいて行われる。しかし MGAT に関しては、サブタイプも含め、その単結晶構造はもちろん基質もしくは低分子化合物との共結晶構造などの報告例はない。標的タンパクの立体構造が未知である場合、標的タンパクに作用する基質や薬物（リガンド）の構造情報を基に、化合物の特定部位に存在する官能基を変換する試みがなされている。従って、標的タンパクに作用する部位の特定はリード化合物を最適化する上で重要な過程を担っている。HTS ヒット化合物 **1** の周辺化合物の情報から、標的タンパクに作用する部位としてスルホンアミド窒素に置換するベンゼン環上のオルト位とパラ位の置換基の導入が考えられた。これは AstraZeneca 社の化合物の構造活性相関[26]と類似しており、これらの化合物が MGAT2 の同じ結合ポケットで相互作用していることを示唆している。

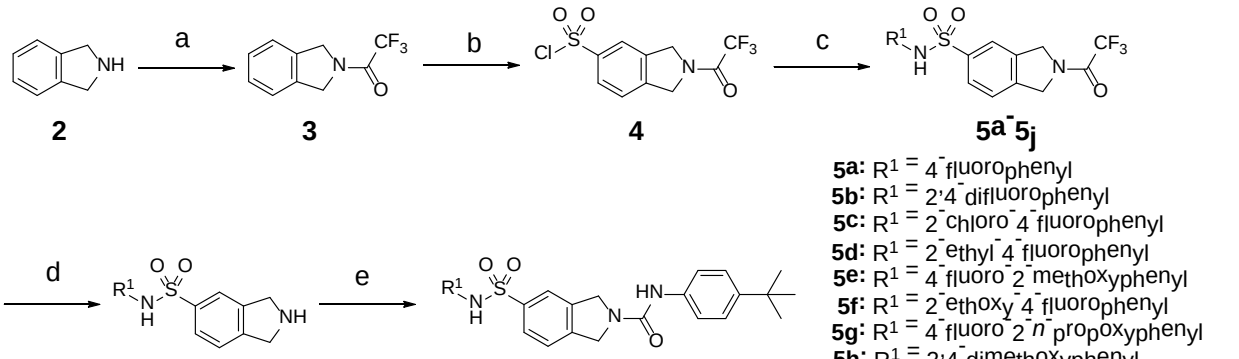
一方、経口投与可能な薬剤を創出する際、化合物の溶解度は消化管から体内への吸収性を考慮する上で重要な要素の一つである。一般的に化合物の溶解度を向上するには、１）分子の平面性を崩して結晶パッキングを崩壊することにより化合物間の相互作用を減弱させる[29-31]、２）極性基の導入および脂溶性の低減により化合物と溶媒の相互作用を向上させる[32]、３）結晶形・粒子状態を変えることにより溶解速度を向上させる[33]、といった手法がとられる。筆者は化合物 **1** の低溶解性は、分子の平面性が高いことでより強固な結晶パッキングが形成されているためであると推察した。

以上のような理由から、筆者は化合物 **1** の MGAT2 阻害活性を向上させ、かつ溶解度を改善するため、まずスルホンアミド窒素に置換するベンゼン環のオルト位およびパラ位の置換基変換を行い、次にイソインドリン骨格の変換やウレア結合部位を変換することで酵素阻害活性および溶解度に対する効果を検証した。

第２節　イソインドリン誘導体の合成と構造活性相関

化合物 **1** および化合物 **1** のスルホンアミド窒素に置換するベンゼン環上の置換基を変換した化合物 **7b**－**7j** は、Scheme 1 に示すように種々のアニリンを用いて合成した。出発原料のイソインドリン **2** をトリフルオロアセチル基で保護した化合物 **3** に対し、クロロスルホン酸を作用させてスルホニルクロリド **4** を得た。このスルホニルクロリド **4** に対し、種々のアニリンを作用させてスルホンアミド誘導体 **5a**－**5j** に変換した。塩基性条件下でトリフルオロアセチル基を脱保護し、(4-*tert*-butylphenyl)isocyanate とそれぞれ縮合することで化合物 **1** およびイソインドリン誘導体 **7b**－**7j** を合成した。

Scheme 1



5a: R^1 = 4-fluorophenyl
5b: R^1 = 2,4-difluorophenyl
5c: R^1 = 2-chloro-4-fluorophenyl
5d: R^1 = 2-ethyl-4-fluorophenyl
5e: R^1 = 4-fluoro-2-methoxyphenyl
5f: R^1 = 2-ethoxy-4-fluorophenyl
5g: R^1 = 4-fluoro-2-*n*-propoxyphenyl
5h: R^1 = 2,4-dimethoxyphenyl
5i: R^1 = 2-fluoro-4-methoxyphenyl
5j: R^1 = 2-fluoro-4-(*n*-pentyloxy)phenyl

6a: R^1 = 4-fluorophenyl
6b: R^1 = 2,4-difluorophenyl
6c: R^1 = 2-chloro-4-fluorophenyl
6d: R^1 = 2-ethyl-4-fluorophenyl
6e: R^1 = 4-fluoro-2-methoxyphenyl
6f: R^1 = 2-ethoxy-4-fluorophenyl
6g: R^1 = 4-fluoro-2-*n*-propoxyphenyl
6h: R^1 = 2,4-dimethoxyphenyl
6i: R^1 = 2-fluoro-4-methoxyphenyl
6j: R^1 = 2-fluoro-4-(*n*-pentyloxy)phenyl

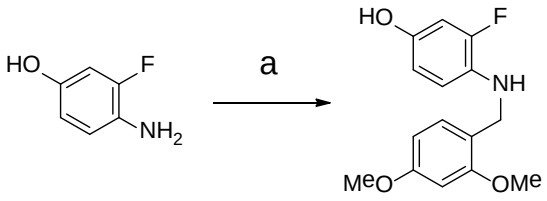
1: R^1 = 4-fluorophenyl
7b: R^1 = 2,4-difluorophenyl
7c: R^1 = 2-chloro-4-fluorophenyl
7d: R^1 = 2-ethyl-4-fluorophenyl
7e: R^1 = 4-fluoro-2-methoxyphenyl
7f: R^1 = 2-ethoxy-4-fluorophenyl
7g: R^1 = 4-fluoro-2-*n*-propoxyphenyl
7h: R^1 = 2,4-dimethoxyphenyl
7i: R^1 = 2-fluoro-4-methoxyphenyl
7j: R^1 = 2-fluoro-4-(*n*-pentyloxy)phenyl

Reagents and conditions: (a) TFAA, pyridine, DMAP, $CHCl_3$, rt, 99%; (b) $ClSO_3H$, $CHCl_3$, rt, 71%; (c) R^1NH_2, pyridine, DMAP, $CHCl_3$, rt, 34-95%; (d) KOH aq., EtOH, rt; (e) (4-*tert*-butyl-phenyl)isocyanate, Et_3N, $CHCl_3$-DMSO, rt, 32-84% in two steps.

また、スルホンアミド窒素に置換するベンゼン環のパラ位アルコキシ誘導体 **12a**－**12c**

の合成は、スルホンアミド窒素を保護した共通フェノール中間体に対してアルキルハライドを作用させることで合成した。アルキル化反応においてフェノールの水酸基のみを反応させるため、スルホンアミド窒素を保護することが必要となる。したがって、共通フェノール中間体は 4-amino-3-fluorophenol（**8**）のアミノ基を保護したアニリンを用いて合成した。アミノ基の保護基として以下の観点から 2,4-ジメトキシベンジル基を選択した。すなわち、アニリン窒素原子の求核力を保ちつつ塩基性条件下で安定であること、かつスルホンアミド体に誘導化した後に酸性条件下で脱保護可能であるという点である。化合物 **8** と 2,4-dimethoxybenzaldehyde との還元的アミノ化反応により化合物 **9** を合成した（Scheme 2）。

Scheme 2

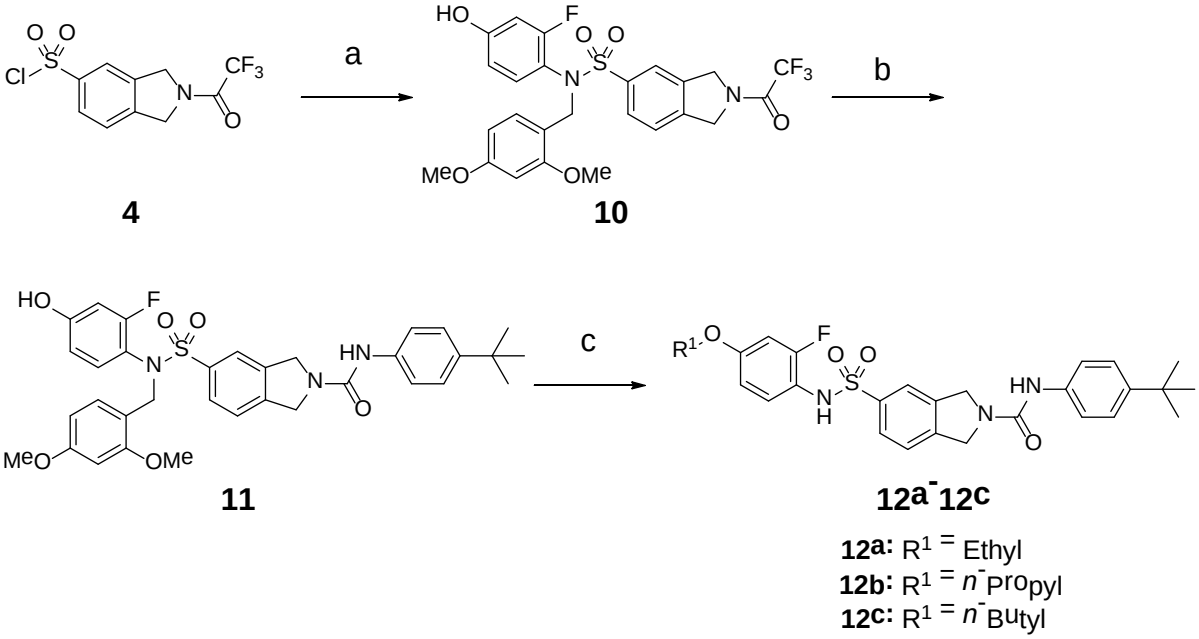


8 **9**

Reagents and conditions: (a) 2,4-dimethoxybenzaldehyde, $NaBH(OAc)_3$, AcOH, THF, rt, 92%.

Scheme 3 に示すように、酸クロリド **4** とアニリン **9** を縮合することでスルホンアミド基を保護した中間体 **10** とし、トリフルオロアセチル基の除去および(4-*tert*-butylphenyl)-isocyanate との縮合を行い、共通フェノール中間体 **11** を得た。この中間体 **11** に対して種々のアルキルハライドを作用させた後に、酸性条件下、脱保護することでアルコキシ誘導体 **12a**－**12c** を合成した。

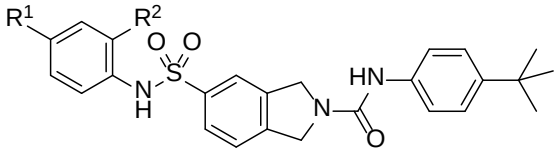
Scheme 3



Reagents and conditions: (a) **9**, pyridine, DMAP, $CHCl_3$, rt, 52%; (b) KOH aq., EtOH, rt, then (4-*tert*-butylphenyl)isocyanate, Et_3N, $CHCl_3$-DMSO, rt, 49%; (c) R^1I, K_2CO_3, DMF, rt, then 10% TFA, $CHCl_3$, rt, 46-68%.

合成したイソインドリン誘導体の **7b**－**7j** および **12a**－**12c** の MGAT2 阻害試験の結果を Table 1 に示す。

Table 1. Structure-activity relationships of 2,3-dihydro-1*H*-isoindole-5-sulfonamide derivatives



Compound	R^1	R^2	hMGAT2 IC_{50}[a] (nM)
1	F	H	594
7b	F	F	685
7c	F	Cl	1110
7d	F	Et	2490
7e	F	MeO	168
7f	F	EtO	733
7g	F	*n*-PrO	2300
7h	MeO	MeO	3160
7i	MeO	F	164
12a	EtO	F	5200
12b	*n*-PrO	F	1980
12c	*n*-BuO	F	547
7j	*n*-penO	F	147

[a] Values are the means of two or more separate experiments.

化合物 **1** と比較して、オルト位にフッ素原子を導入した化合物 **7b** は活性を保持したが（**1** vs **7b**）、クロロ基およびエチル基を導入した化合物では活性が 2 から 5 倍程度低下した（**1** vs **7c** and **7d**） 。しかしながら、化合物 **1** のオルト位にメトキシ基を導入した化合物 **7e** は、化合物 **1** と比べて約 3 倍活性が向上した（**1** vs **7e**）。このオルト位において、エトキシ基や *n*-プロポキシ基のようにアルコキシ基の長さを伸張したところ、活性が低下する結果となった（**7e** vs **7f** and **7g**）。2,4-ジメトキシフェニル誘導体 **7h** は **7e** と比較して大幅な活性の低下が見られたが（**7e** vs **7h**）、興味深いことに 2-フルオロ-4-

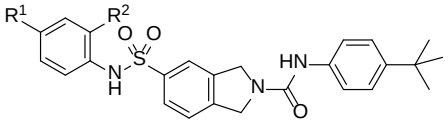
メトキシフェニル誘導体 **7i** は、**7e** と同等の活性が見られることが明らかとなった（**7e** vs **7i**）。化合物 **7i** のメトキシ基をエトキシ基に変換した化合物 **12a** は酵素阻害活性が低下し、これはオルト位のアルコキシ基を伸張した場合と同じ結果であった。オルト位の置換基変換において、*n*-プロポキシ誘導体は対応するエトキシ誘導体よりもより活性が低下した（**7f** vs **7g**）が、パラ位においては *n*-プロポキシ誘導体 **12b** の酵素阻害活性がエトキシ誘導体の活性よりも増強した（**12a** vs **12b**）。パラ位についてはアルコキシ基の炭素鎖を伸張すればするほど、より活性が向上した（**12c** and **7j**）。

以上の結果から、筆者は化合物 **1** のスルホンアミド窒素に置換するベンゼン環上の置換基が MGAT2 阻害活性に重要な役割を担っている部位であることを明らかにした。特にスルホンアミド側鎖として、ベンゼン環上のパラ位に炭素鎖の長い官能基を導入すると酵素阻害活性が向上したことから、標的タンパクと疎水性相互作用するポケットの存在が示唆された。

第３節　イソインドリン誘導体のプロファイルとマウス薬物動態試験

化合物 **1** よりも活性の向上した代表的な化合物（**7e**、**7i**、**7j**）について、溶解度および肝代謝安定性を測定した（Table 2）。実際の腸管では胆汁酸をはじめとする可溶化成分が分泌されていると考えられており、溶解度の測定に食後の消化管内環境を模倣した緩衝液（FeSSIF）を用いた[34]。化合物 **1** と比較して化合物 **7e** は溶解度の向上が認められたが、化合物 **7i** および **7j** は水に対する溶解度に関して改善は見られなかった。これらの結果から、スルホンアミド窒素に置換するベンゼン環のオルト位に小さな置換基や親水基の導入では溶解度の改善に大きな影響を与えないということが判明した。代謝安定性については、化合物 **1** はヒトミクロソームに対して安定であったが、マウスミクロソームについては代謝されやすいことが明らかとなった。他の化合物についても同様な

Table 2. Inhibitory activity for MGAT2 enzyme, solubility, and metabolic stability in microsomes of selected compounds



Compound	R^1	R^2	hMGAT2 IC_{50}[a] (nM)	Solubility (μg/mL) Water / FeSSIF[b]	MS[c] (h/m) (%)
1	F	H	594	<0.07 / NT[d]	12.3 / 70.9
7e	F	MeO	168	0.607 / 28.3	43.1 / 60.6
7i	MeO	F	164	<0.06 / 0.783	20.6 / 51.1
7j	*n*-PenO	F	147	<0.06 / 10.2	0.1 / 12.6

[a] Values are the means of two or more separate experiments.

[b] Fed State Simulated intestinal Fluid, pH 5.0.

[c] %Metabolized after 15 min of incubation with human/mouse liver microsomes.

[d] NT: Not tested.

傾向であったが、これらの化合物のうち化合物 **7j** はヒトおよびマウスミクロソームにおいて最も安定な結果となった。

溶解度が向上した化合物 **7e** のマウス血漿中濃度を測定した。その血漿中濃度推移を Figure 8 に示す。

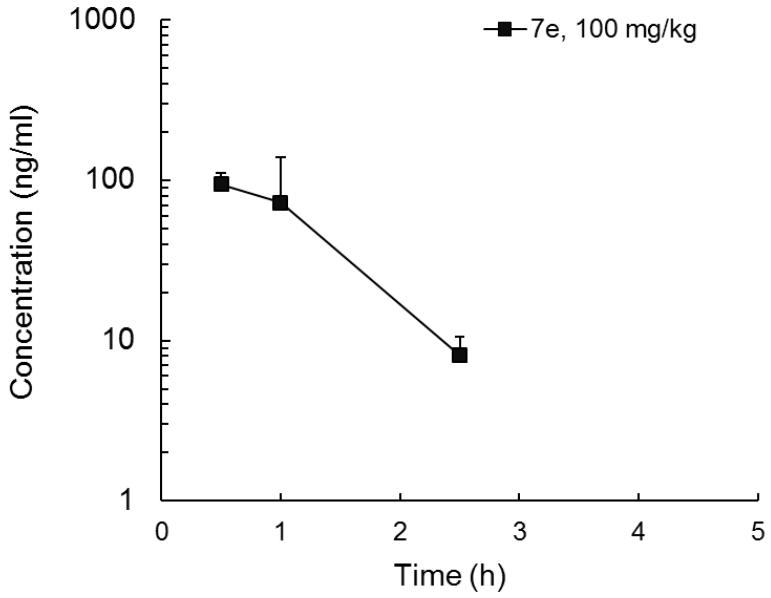


Figure 8. Plasma exposure for **7e** after orally dosing at 100 mg/kg as a 0.5% MC solution to mice; n = 3 per group. Values are means ± SEM.

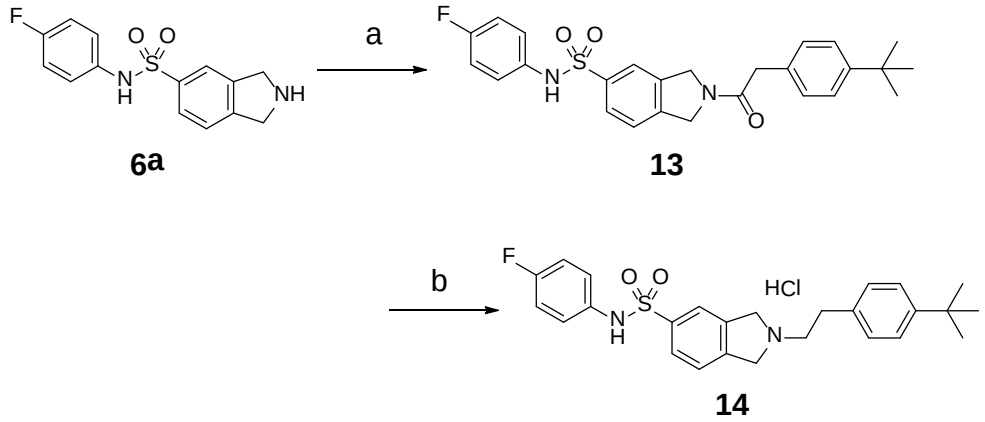
化合物 **7e** を 100 mg/kg の用量で経口投与したところ、血中曝露量は極めて低い結果であった（C_{max}：94.3 ng/mL、$AUC_{0–4h}$：134 ng•h/mL）。化合物 **7e** の血中曝露量が低い原因として、溶解度が不十分なために化合物が吸収されにくいことや、マウスミクロソームによる代謝の影響を受けやすいことから吸収後に速やかに化合物が消失してしまうことなどが考えられる。

続いて筆者は、イソインドリン骨格やウレア結合部位を変換することによる酵素阻害活性および溶解度に対する効果について検証した。

第４節　イソインドリン誘導体の母格およびリンカー変換による溶解度の向上

化合物 **1** のウレア結合を変換した化合物は、Scheme 4 に示すように中間体 **6a** を用いて合成した。すなわち、中間体 **6a** を(4-*tert*-butylphenyl)acetic acid と縮合し、アミド化合物 **13** を得た。*N*-アルキル化合物 **14** は、化合物 **13** のアミド基を還元することで合成した。

Scheme 4

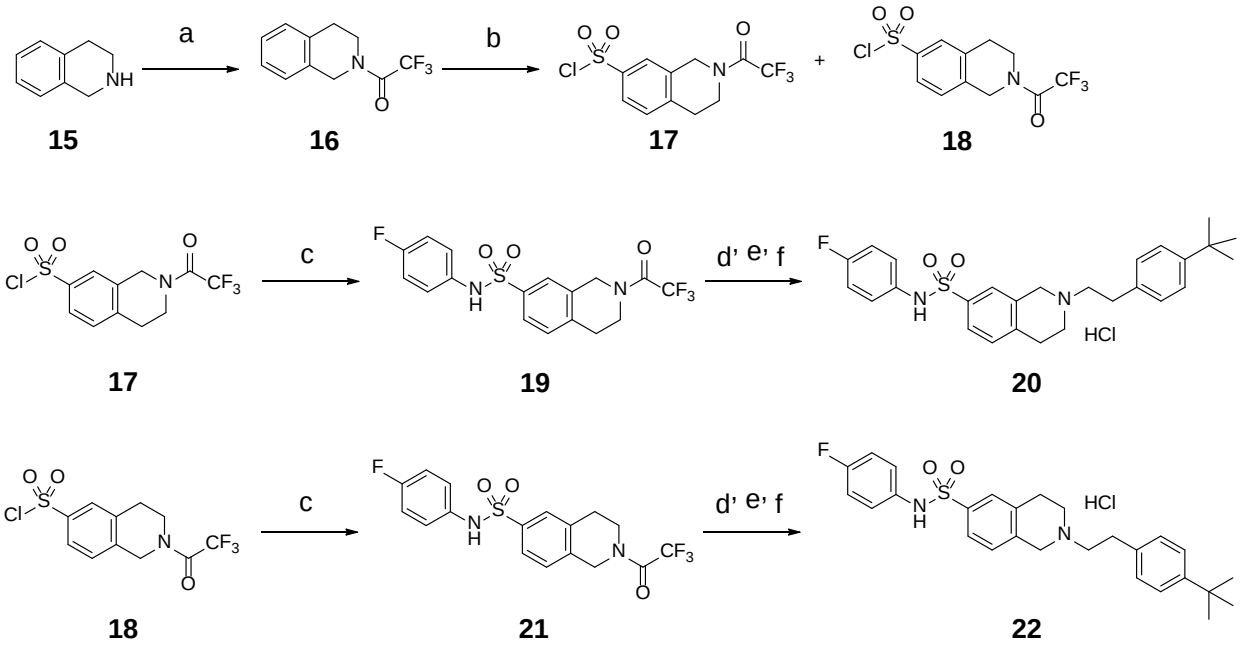


6a　　**13**　　**14**

Reagents and conditions: (a) (4-*tert*-butylphenyl)acetic acid, EDC・HCl, HOBt・H_2O, $CHCl_3$, rt, 29%; (b) BH_3・THF, THF, 90 °C, then 4M HCl/EtOAc, EtOAc, rt, 30%.

化合物 **1** のイソインドリン骨格の変換は、テトラヒドロイソキノリン **15** を出発原料として合成した（Scheme 5）。2 級アミン部位をトリフルオロアセチル基で保護し、次いでクロロスルホニル化反応を行い、得られた位置異性体混合物（**17** および **18**）をシリカゲルカラムクロマトグラフィーによりそれぞれ単離した [35]。これら中間体を 4-fluoroaniline と縮合し、塩基性条件下脱保護を行った後に、化合物 **14** の合成と同様の手法で化合物 **20** および **22** をそれぞれ合成した。

Scheme 5

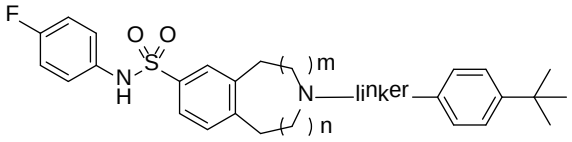


Reagents and conditions: (a) TFAA, pyridine, DMAP, $CHCl_3$, rt, 89%; (b) $ClSO_3H$, $CHCl_3$, rt, 59% for **17**, 14% for **18**; (c) 4-fluoroaniline, pyridine, DMAP, $CHCl_3$, rt, 92%; (d) KOH aq., EtOH, rt; (e) (4-*tert*-butylphenyl)acetic acid, EDC・HCl, HOBt・H_2O, $CHCl_3$, rt; (f) BH_3・THF, THF, 90 °C, then 4M HCl/EtOAc, EtOAc, rt, 36-50% in three steps.

合成した化合物（**13**、**14**、**20** および **22**）の酵素阻害活性および溶解度の結果を Table 3 に示す。

ウレア結合からアミド結合に変換した化合物 **13** は水への溶解度に対して変化は見られなかった（**1** vs **13**）のに対し、エチレン基に変換した化合物 **14** は化合物 **1** と比較して酵素阻害活性が 4 倍程度減弱するものの、溶解度が向上する結果となった（**1** vs **14**）。この化合物 **14** のイソインドリン骨格をテトラヒドロイソキノリン骨格に変換した化合物 **22** は、酵素阻害活性を保持したまま化合物 **14** より更に溶解度が向上した。

Table 3. Inhibitory activity for MGAT2 and solubility of 2,3-dihydro-1*H*-isoindole-5-sulfonamide analogs with the linker and scaffold modification of compound **1**



Compound	m	n	linker	hMGAT2 IC_{50}[a] (nM)	Solubility (μg/mL) Water / FeSSIF[b]
1	0	0	—CONH—	594	<0.07 / NT[c]
13	0	0	—$COCH_2$—	8070	<0.11 / NT[c]
14	0	0	—CH_2CH_2—	2120	270 / NT[c]
20	0	1	—CH_2CH_2—	3060	NT[c] / NT[c]
22	1	0	—CH_2CH_2—	1522	641 / 385

[a] Values are the means of two or more separate experiments.

[b] Fed State Simulated intestinal Fluid, pH 5.0.

[c] NT: Not tested.

以上の結果から、ウレア結合からエチレン鎖に変換し、イソインドリン骨格からテトラヒドロイソキノリン骨格に変換することで、溶解度が改善することを明らかにした。

第５節　新規テトラヒドロイソキノリン誘導体のマウス薬物動態試験と in vivo 薬効試験

第 4 節で述べたように、より溶解度の向上した MGAT2 阻害剤 **22** を見出したので、本化合物のマウス血漿中濃度を測定した。その結果を Figure 9 に示す。

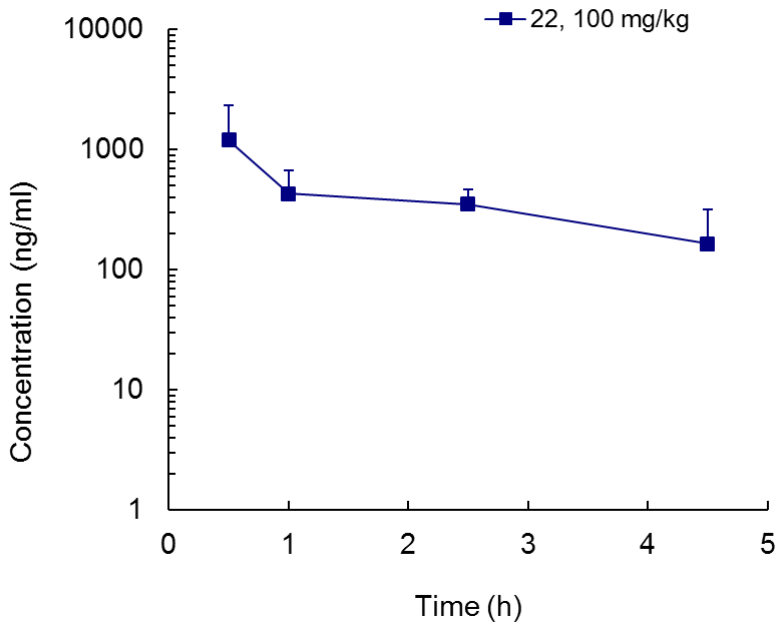


Figure 9. Plasma exposure for **22** after orally dosing at 100 mg/kg as a 0.5% MC solution to mice; n = 3 per group. Values are means ± SEM.

100 mg/kg の用量で化合物 **22** をマウスに経口投与したところ、血中曝露量が化合物 **7e** と比較して 10 倍以上向上することが明らかとなった（C_{max}：1200 ng/mL、$AUC_{0–4h}$：1808 ng•h/mL）。

マウス脂肪負荷試験（OLTT）の薬理作用を確認するため、化合物 **22** のマウス MGAT2 阻害活性（mMGAT2）および肝代謝安定性試験を実施した（Table 4）。化合物 **22** はマウス MGAT2 に対してもヒト MGAT2 と同等の阻害活性を示した。また、化合物 **7e** と比較して、ヒトミクロソームに対してはより安定であったが、マウスミクロソームに対して

はほぼ同等の安定性であった。この結果から、マウスにおける化合物 **22** の血中曝露量の向上は、化合物の溶解度改善により吸収性が向上したためと考察している。

Table 4. Inhibitory activity for MGAT2 enzyme, metabolic stability in microsomes, and solubility of compound **22**

Compound	hMGAT2 IC_{50}[a] (nM)	mMGAT2 IC_{50}[a] (nM)	MS[b] (h/m) (%)	Solubility (μg/mL) Water / FeSSIF[c]
22	1522	1170	14˙6 / 47˙8	641 / 385

[a] Values are the means of two or more separate experiments.

[b] %Metabolized after 15 min of incubation with human/mouse liver microsomes.

[c] Fed State Simulated intestinal Fluid, pH 5.0.

マウス脂肪負荷試験（OLTT）における化合物 **22** の薬理効果を検討した。その結果を Figure 10 に示す。

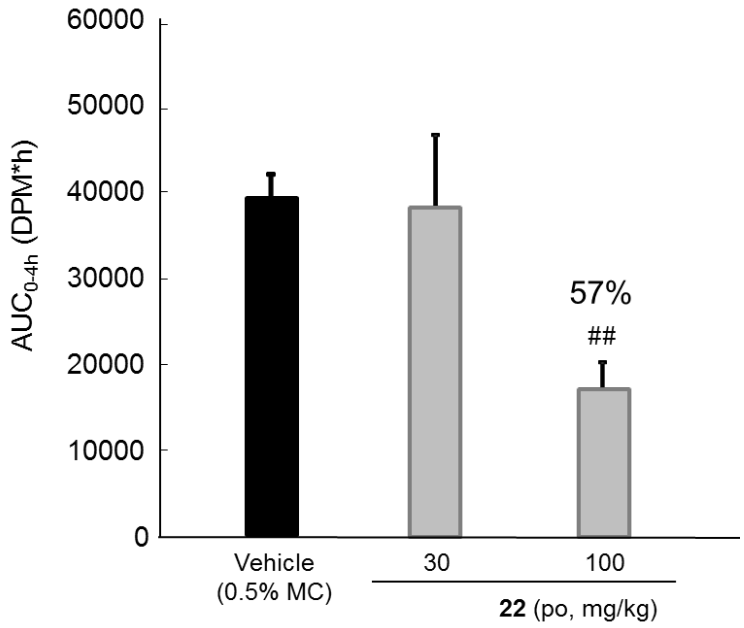


Figure 10. Fat absorption inhibition of compound **22**; n = 7 per group. Values are means±SEM (##, *P*<0.01 versus vehicle group in the Steel's test).

本試験は化合物の経口投与 30 分後にトリグリセリド（TG）を経口投与し、TG 投与の 0.5、1、2 および 4 時間後に血漿中の TG 量を $AUC_{0\text{-}4h}$ 値として算出するものである。化合物 **22** を 100 mg/kg の用量で投与した投与群は、溶媒投与群と比較して有意に血中 TG 量を低下させることが明らかとなった。この結果は、化合物 **22** が有意に脂肪吸収を抑制していることを示している。

第６節　小括

HTS ヒット化合物 **1** より MGAT2 酵素に対する活性を高めながらその溶解度を改善するために構造変換を行った。化合物 **1** のスルホンアミド窒素に置換するベンゼン環上のオルト位の置換基導入は、活性の増強は認められたものの溶解度の改善に大きな影響は与えなかった。一方、イソインドリン骨格およびウレア結合を変換することで、溶解度とマウス血漿中濃度を改善したテトラヒドロイソキノリン誘導体 **22** を見出した。化合物 **22** はマウス脂肪負荷試験において 100 mg/kg の用量で経口投与すると、有意な脂肪吸収抑制効果を示した。

経口投与可能な脂肪吸収抑制作用を有する新規テトラヒドロイソキノリン誘導体 **22** を創出したことから、筆者は更に強力な MGAT2 阻害剤を見出すべく最適化検討を行った。

第２章　強力な MGAT2 阻害活性を有するテトラヒドロイソキノリン誘導体の創出

第１節　テトラヒドロイソキノリン誘導体の合成および構造活性相関

第 1 章の第 2 節で述べたように、イソインドリン誘導体の構造活性相関からスルホンアミド窒素に置換するベンゼン環パラ位の置換基変換において、アルコキシ基の炭素鎖が酵素阻害活性向上に寄与することが考察された（Figure 11, **12a** vs **7j**）。しかしイソインドリン誘導体は低溶解性であり、マウス経口投与後の血中曝露量が極めて低い結果であった。一方、テトラヒドロイソキノリン骨格を持つ化合物 **22** はイソインドリンーウレア骨格と比較し水への溶解度が向上し、その結果、経口吸収性が改善されることを明らかにした。

以上の知見から、経口投与での in vivo 薬効がより低用量で認められる MGAT2 阻害剤を開発するため、テトラヒドロイソキノリン骨格を持つ化合物 **22** のスルホンアミド窒素に置換するベンゼン環のパラ位側鎖の最適化を開始した。

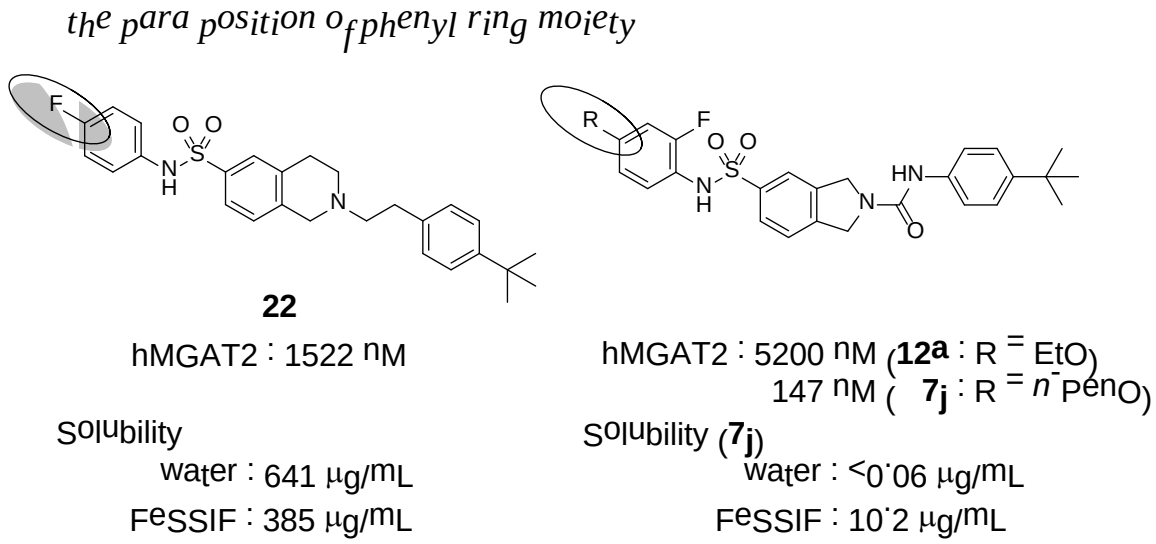
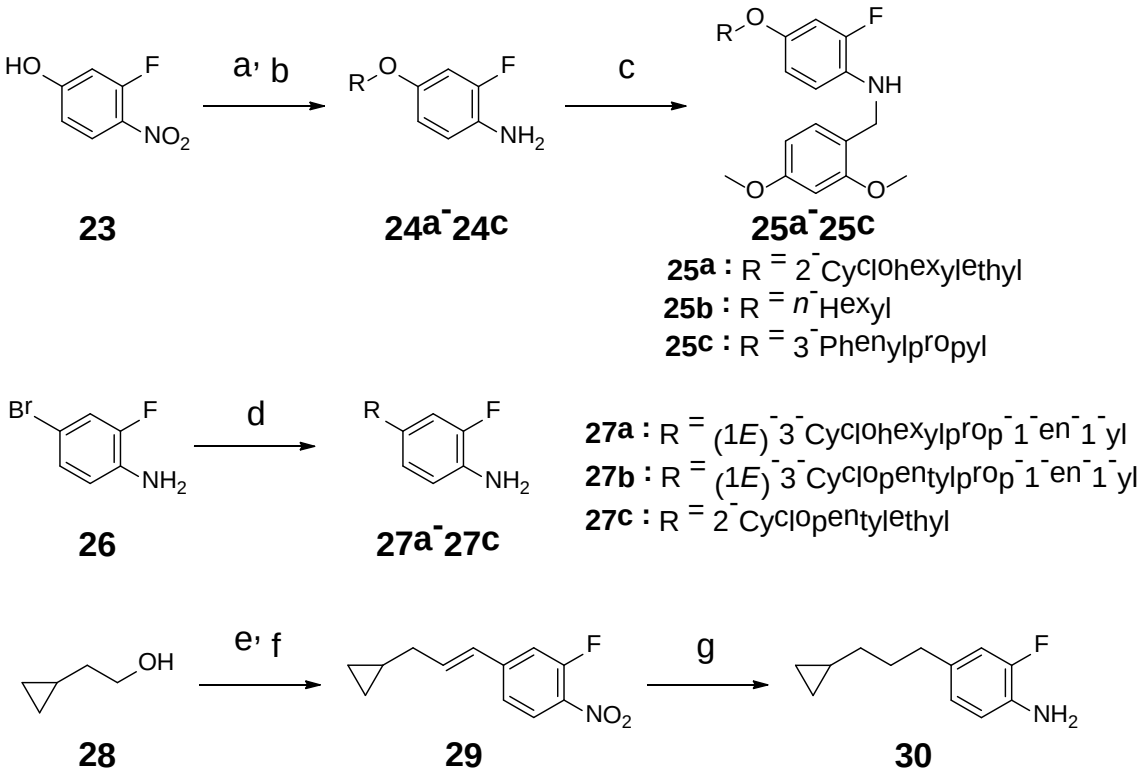


Figure 11. MGAT2 inhibitory activity of tetrahydroisoquinoline and dihydro-1*H*-isoindole sulfonamide derivatives.

テトラヒドロイソキノリン誘導体の合成は、第 1 章で述べたイソインドリン誘導体の合成と同様の手法を用いて行った。誘導体合成を行うにあたり、まず Scheme 6 に示すように各種アニリンを合成した。

Scheme 6



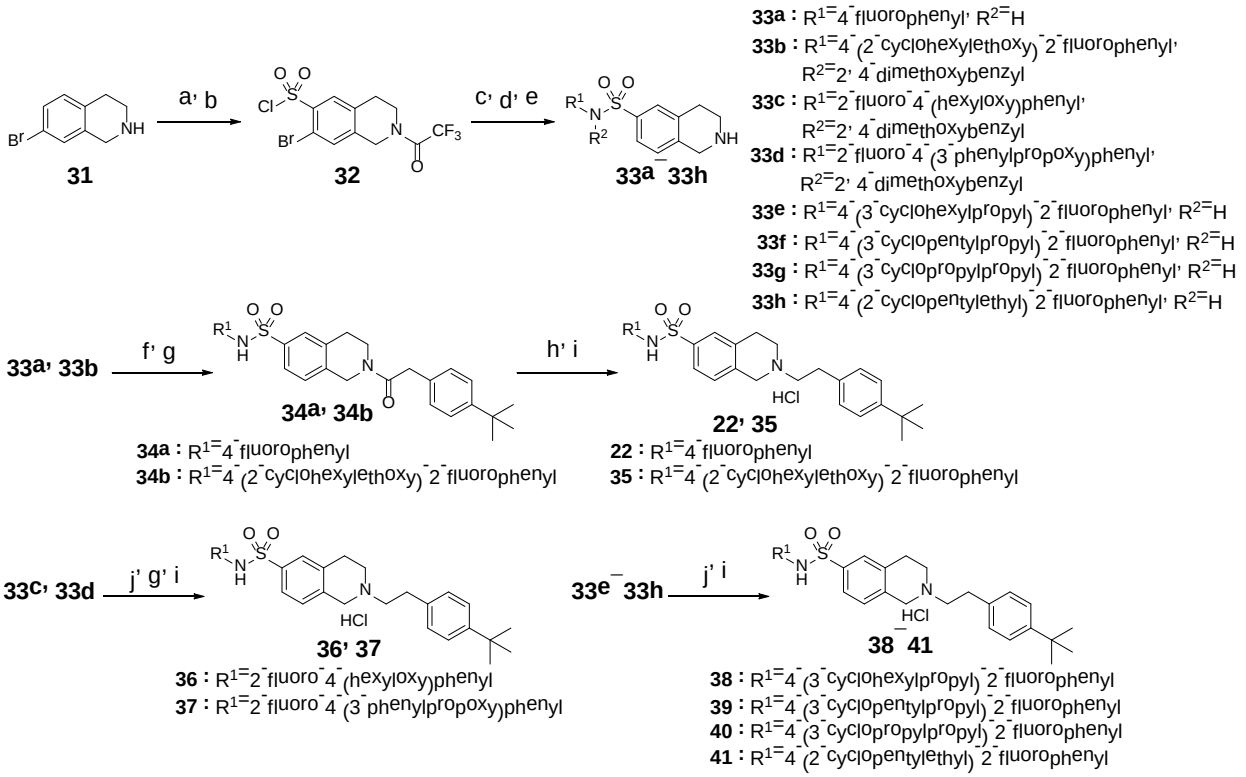
Reagents and conditions: (a) RX, K_2CO_3, DMF, rt; (b) H_2, 10% Pd-C, EtOH, rt, 55-81% in two steps; (c) 2,4-dimethoxybenzaldehyde, $NaBH(OAc)_3$, AcOH, THF, rt, 34%-quant.; (d) olefin or borane reagent, Pd catalyst, solvent, reflux, 69-92%; (e) PPh_3, I_2, imidazole, $CHCl_3$, rt; (f) PPh_3, CH_3CN, reflux, then 3-fluoro-4-nitrobenzaldehyde, KHMDS, THF, rt, 37% in two steps; (g) H_2, 10% Pd-C, EtOH, rt, 57%.

アニリン **24a**－**24c** は出発原料である 3-fluoro-4-nitrophenol（**23**）に対して対応するアルキルハライドを作用させ、次いでニトロ基を還元することで得た。これらのアニリンを 2,4-dimethoxybenzaldehyde との還元的アミノ化反応に付しアニリン **25a**－**25c** へと導いた。アニリン **27a**－**27c** はアニリン **26** に対し、対応するオレフィンやボラン試薬を用

いて Pd 触媒存在下、Heck 反応あるいは鈴木－宮浦カップリング反応によりそれぞれ合成した。また、アルコール **28** から誘導した対応するヨウ化アルキルをフォスフォニウム塩へと誘導し、3-fluoro-4-nitrobenzaldehyde と Wittig 反応を行い化合物 **29** に変換し、このニトロ基およびオレフィン部位を還元することによりアニリン **30** を得た。

合成したアニリンを用いて、Scheme 7 に示すルートにてテトラヒドロイソキノリン誘導体を合成した。出発原料である 7-bromo-1,2,3,4-tetrahydroisoquinoline（**31**）の 2 級アミンを無水トリフルオロ酢酸で保護し、クロロスルホニル化反応により中間体 **32** を得た。この中間体 **32** に対して、対応するアニリンと縮合した後に水素添加による脱ブロモ化反応、次いで塩基性条件下、脱トリフルオロアセチル化反応を行い中間体 **33a**－**33h** とした。2 級アミン中間体 **33a** および **33b** を(4-*tert*-butylphenyl)acetic acid と縮合した後、酸性条件下、2,4-ジメトキシベンジル基の脱保護を行いアミド化合物 **34a** および **34b** を得た。*N*-アルキル化合物 **22** および **35** は、化合物 **34a** および **34b** のアミド基をボラン還元することで合成した。他の中間体 **33c**－**33h** は(4-*tert*-butylphenyl)acetaldehyde との還元的アミノ化反応により、対応する *N*-アルキル誘導体 **36**－**41** に変換した。

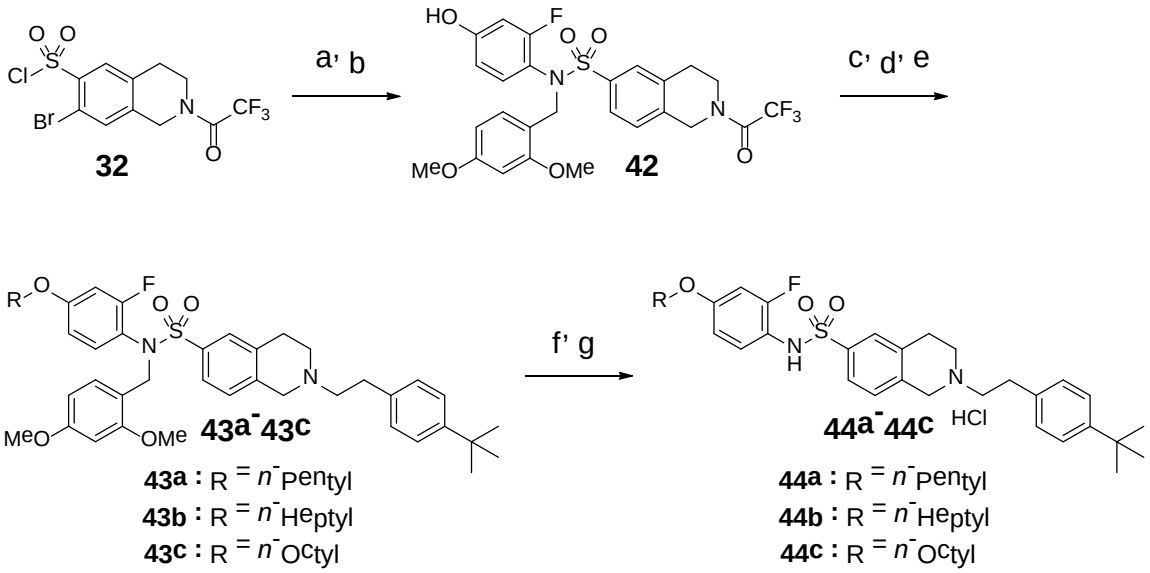
Scheme 7



Reagents and conditions: (a) TFAA, pyridine, DMAP, $CHCl_3$, rt; (b) $ClSO_3H$, $CHCl_3$, 60 °C, 69% in two steps; (c) R^1R^2NH, pyridine, $CHCl_3$, rt; (d) H_2, 10% Pd-C, MeOH-EtOAc, rt; (e) KOH aq., EtOH, rt, 61-94% in three steps; (f) (4-*tert*-butylphenyl)acetic acid, EDC・HCl, HOBt・H_2O, $CHCl_3$, rt, 59% for **34a**; (g) 10% TFA, $CHCl_3$, rt, 54% in two steps for **34b**; (h) BH_3・THF, THF, relux; (i) 4M HCl/EtOAc, EtOAc, rt, 91 and 45% in two steps for **22** and **35**, 65% and 63% in three steps for **36** and **37**, 56-84% in two steps for **38**-**41**; (j) (4-*tert*-butyl-phenyl)acetaldehyde, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt.

アルコキシ誘導体 **44a**－**44c** は、2,4-ジメトキシベンジル基で保護したアニリン **9** を用いて合成した（Scheme 8）。スルホニルクロリド **32** とアニリン **9** を縮合後に Pd-C を用いて脱ブロモ化反応を行い、スルホンアミド中間体 **42** を得た。中間体 **42** に対応するアルキルハライドを作用させ、トリフルオロアセチル基の除去および(4-*tert*-butylphenyl)acetaldehyde との還元的アミノ化反応を行うことで *N*-アルキル中間体 **43a**－**43c** を得た。これらを酸性条件下、脱保護することでアルコキシ誘導体 **44a**－**44c** を合成した。

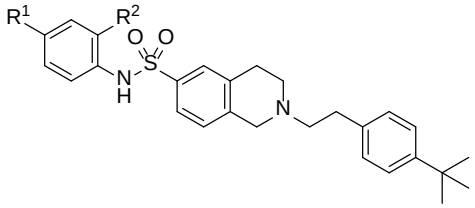
Scheme 8



Reagents and conditions: (a) **9**, pyridine, $CHCl_3$, rt; (b) H_2, 10% Pd-C, Et_3N, MeOH-EtOAc, rt, 70% in two steps; (c) RI, K_2CO_3, DMF, rt; (d) KOH aq., EtOH, rt; (e) (4-*tert*-butylphenyl)acetaldehyde, $NaBH(OAc)_3$, $CHCl_3$, rt, 36-68% in three steps; (f) 20% TFA, $CHCl_3$, rt; (g) 4M HCl/EtOAc, EtOAc, rt, 2-33% in two steps.

合成したイソインドリン誘導体の **35**－**41** および **44a**－**44c** の MGAT2 阻害試験の結果を Table 5 に示す。予期したとおり、化合物 **7j** と同じ置換基を導入した化合物 **44a** は、化合物 **22** と比べて約 3 倍活性が向上した。*n*-ヘキシルオキシ基や *n*-ヘプチルオキシ基のようにアルコキシ基の炭素鎖を更に伸張するとさらに活性が増強した（**36** and **44b**）が、*n*-オクチルオキシ誘導体 **44c** は、*n*-ヘプチルオキシ誘導体 **44b** と同等の活性に留まった。側鎖の末端部位にベンゼン環を導入した化合物 **37** は活性を保持した。ベンゼン環をシクロヘキサン環に変換した化合物 **35** は活性が増強し（**35** vs **37**）、エーテルリンカーをメチレンリンカーに変換した化合物 **38** では、活性が保持する結果であった（**35** vs **38**）。

Table 5. Structure-activity relationships of tetrahydroisoquinoline derivatives with a variety of substituents at the *para* position



Compound	R^1	R^2	hMGAT2 IC_{50}[a] (nM)
22	F	H	1522
44a	*n*-PenO	F	454
36	*n*-HexO	F	133
44b	*n*-HepO	F	40
44c	*n*-OctO	F	45
37	$PhCH_2CH_2CH_2O$	F	173
35	*c*-HexCH_2CH_2O	F	76
38	*c*-Hex$CH_2CH_2CH_2$	F	62
39	*c*-Pen$CH_2CH_2CH_2$	F	28
40	*c*-Pr$CH_2CH_2CH_2$	F	379
41	*c*-PenCH_2CH_2	F	10000

[a] Values are the means of two or more separate experiments.

シクロアルカン部位の環の大きさを比較したところ、末端にシクロペンチル基を導入した化合物 **39** が最も強力な MGAT2 阻害剤であることが判明した（IC_{50} = 28 nM）。このシクロペンチル基をシクロプロピル基に変換した化合物や炭素鎖を短縮した化合物では、化合物 **39** に比べて活性が大幅に低下した（**39** vs **40** and **41**）。

第２節　テトラヒドロイソキノリン誘導体の in vivo 薬効試験と化合物 **39** の同定

化合物 **22** よりも強力な MGAT2 阻害活性を有する化合物を見出したので、*n*-アルキル基、フェニル基そしてシクロアルキル基のような構造的に異なる置換基を有する化合物（**44c**、**37** および **39**）を選抜して物性および薬理作用に関するプロファイリングを実施した。すなわち、これら選抜化合物のマウス MGAT2 阻害活性、肝ミクロソーム代謝安定性、FeSSIF における溶解度、化合物投与 30 分後のマウス血漿中濃度およびマウス in vivo 脂肪負荷試験（OLTT）における薬理作用について検討した。その結果を Table 6 に示す。

Table 6. Profiles of representative compounds

Compound	MGAT2 IC_{50}[a] (nM) (h/m)	MS[b] (%) (h/m)	Solubility (μg/mL) FeSSIF[c]	Plasma exposure at 0.5 h[d] (ng/mL)	% Reduction of TG in OLTT[e] Dose (mg/kg) 1	3	10	30	100
22	1522 / 1170	14.6 / 47.8	385	135	NT[f]	NT[f]	NT[f]	2%	57%##
44c	45 / 20	-5.2 / -3.5	207	21.5	NT[f]	-10%	22%##	28%$$	NT[f]
37	173 / 25	23.6 / 14.3	68.3	13.9	1%	5%	14%	29%*	NT[f]
39	28 / 4	-9.6 / -4.3	288	54.3	19%	25%**	35%***	38%***	41%***

[a] Values are the means of two or more separate experiments.

[b] %Metabolized after 15 min of incubation with human/mouse liver microsomes.

[c] Fed State Simulated Intestinal Fluid, pH 5.0.

[d] Orally dosed at 30 mg/kg as a 0.5% MC solution to mice.

[e] Data are the mean ± standard error of the mean averaged from 7-8 studies, expressed as percentage reduction of plasma $AUC_{0\text{-}4h}$ levels of TG for 4 h after an oral administration as a 0.5% MC solution in mice fat load test (*; P<0.05, **; P<0.01, ***; P<0.001 vs. vehicle (Dunnett's test), ##; P<0.01 vs. vehicle (Steel's test), $$; P<0.01 vs. vehicle (Student's t-test)).

[f] NT: Not tested.

これらの化合物のマウス MGAT2 に対する阻害活性は、ヒト MGAT2 阻害活性と同様の傾向を示し、化合物 **39** で最も強い阻害活性を示した。また、経口投与 30 分後のマウス

血中曝露量は FeSSIF に対する溶解度と良く相関することが分かった。

次に薬理試験結果について述べる。化合物 **22** は 100 mg/kg の用量で有意な脂肪吸収抑制効果を示したが、これらの化合物の中で最も血中曝露量が高いにも関わらず、30 mg/kg の用量では効果を示さなかった。この結果は化合物 **22** の MGAT2 阻害活性が、30 mg/kg 以下の用量で in vivo 薬効を示すためには不十分であることを示している。一方、化合物 **22** と比較して MGAT2 阻害活性が増強した他の化合物については、30 mg/kg の用量で有意な薬効を示した。化合物 **44c** および **37** に関しては 10 mg/kg 以下の投与用量において効果が減弱したが、化合物 **39** は 3 mg/kg の用量から脂肪吸収抑制作用を示すことが明らかとなった。

第３節　化合物 **39**（**TP0455353**）のマウス薬物動態試験結果

マウス脂肪負荷試験において化合物 **39**（**TP0455353**）は有意な血中 TG 抑制効果を示したので、マウス薬物動態試験を行った。1 mg/kg での静脈投与の結果および 3 mg/kg での経口投与後の結果を Table 7 に示した。

Table 7. PK Pofiles of compound **39** (**TP0455353**) in mice

	CL[a] (mL/h/kg)	Vdss[b] (mL/kg)	$T_{1/2}$ (h)	AUC_{last}[c] (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h}[c] (ng•h/mL)	BA[d] (%)
iv 1 mg/kg	1560	6930	7.1	625	–	–	–	–
po 3 mg/kg	–	–	–	–	127	1.67	402	21.4

[a] CL: clearance
[b] Vdss: volume of distribution
[c] AUC: area under the curve
[d] BA: bioavailability

化合物 **39**（**TP0455353**）の C_{max} および AUC_{0-24h}はそれぞれ 127 ng/mL および 402 ng•h/mL であり、生物学的利用率（BA）は 21.4%であった。化合物 **39**（**TP0455353**）の TG 投与後 4 時間の血中濃度は 43.5 ng/mL（75 nM）であり、in vitro での MGAT2 阻害活性（IC_{50}＝4 nM）と比べ約 18 倍高い曝露値であった。これは 3 mg/kg の用量で有意な脂肪吸収抑制効果を示すことを裏付ける結果であり、MGAT2 阻害を介した薬理作用であることを示唆している。

第４節　小括

経口投与可能な脂肪吸収抑制作用を有する新規テトラヒドロイソキノリン誘導体 **22** のスルホンアミド窒素に置換するベンゼン環上のパラ位置換基を最適化することで、MGAT2 阻害活性の向上した化合物 **44c**、**37** および **39** を見出した。これらの化合物のプロファイリングを行い、30 mg/kg の用量での経口投与 30 分後のマウス血中曝露量は FeSSIF に対する溶解度と良く相関し、溶解度が高いほど化合物の血中曝露量も向上した。これらの化合物は in vivo マウス脂肪負荷試験において 30 mg/kg の用量で脂肪吸収抑制効果を示し、3 mg/kg の用量から有意に脂肪吸収抑制効果を示す化合物 **39**（**TP0455353**）を同定することができた。更なる高次薬理試験や安全性試験に向けて、筆者は化合物 **39**（**TP0455353**）のスケールアップ合成検討を行った。

第３章　化合物 **39**（**TP0455353**）の効率的合成法の開発

第１節　スケールアップ合成における既存合成法の問題点と新規合成法の開発

テトラヒドロイソキノリンは天然物や医薬品に含まれる最も重要なヘテロ環の一つである。数多くのテトラヒドロイソキノリン誘導体が、抗癌作用 [36]や抗菌作用 [37]、降圧作用 [38]、中枢神経系の抑制作用 [39]、そして抗マラリア活性 [40]といった様々な生物活性を有することが報告されている。

第 2 章で述べたように、筆者は化合物 **39**（**TP0455353**）が新規な MGAT2 阻害剤として強力な阻害活性を有し、マウス in vivo 薬効試験において 3 mg/kg の用量から有意な脂肪吸収抑制作用効果を示すことを見出した（Figure 12）。本化合物は他の動物種での薬効試験や反復投与薬効試験などの高次薬効評価試験や安全性試験を行うに値する化合物であり、これら試験実施のために少なくとも 100 g 程度の原薬供給が必要である。

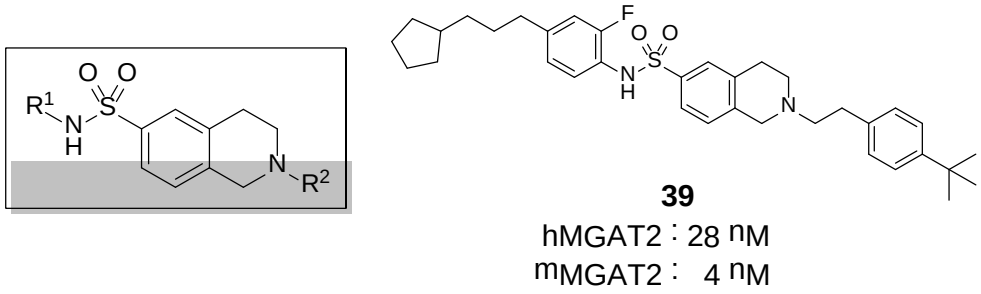
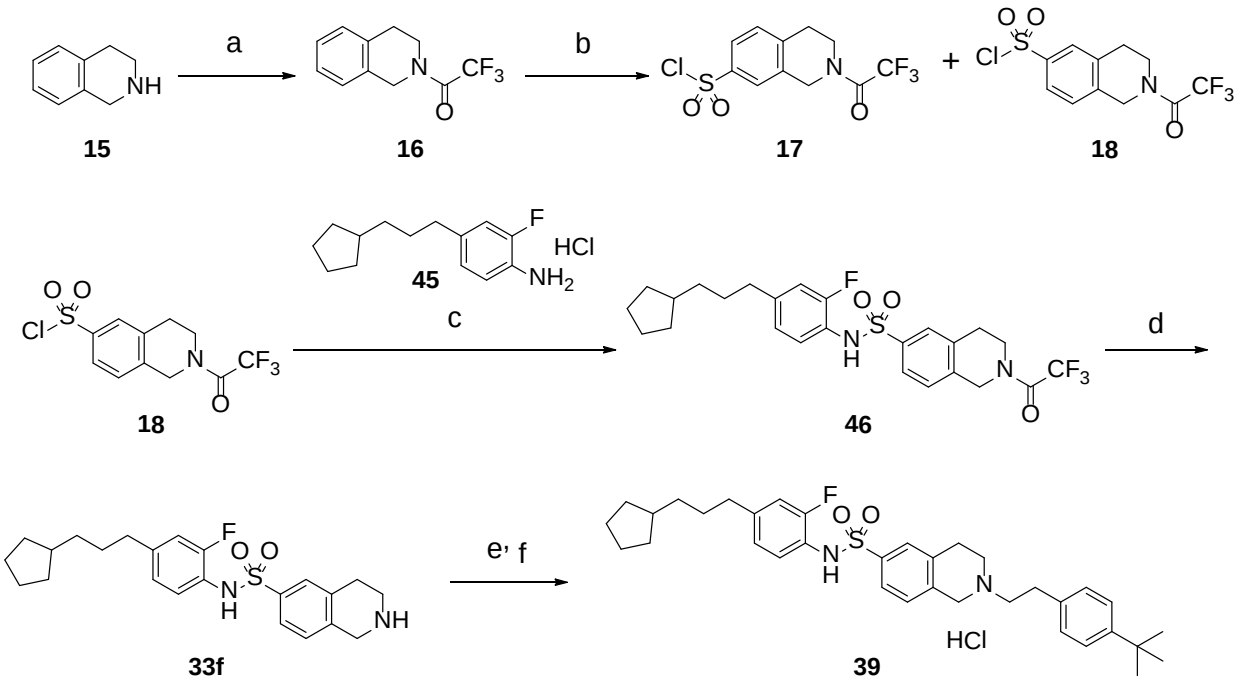


Figure 12. Tetrahydroisoquinoline derivatives and a potent MGAT2 inhibitor **39** (**TP0455353**).

化合物 **39**（**TP0455353**）の初期合成ルートについては、スケールアップ合成において困難な課題があった。具体的には Scheme 9 に示すように、中間体 **16** に対するクロロスルホニル化反応における位置選択性が低いため [35]、目的物 **39**（**TP0455353**）の総収率が 6.8%に留まるということであった。さらに中間体 **17** と **18** の分離精製を行わなければな

らず、煩雑なカラム精製が必要であった。この中間体 **17** と **18** の構造は NOE を測定することでそれぞれ決定した。中間体 **17** の芳香族プロトン（Ha）あるいは中間体 **18** の芳香族プロトン（Hb）と 1 位のメチレン鎖のプロトンとの間で NOE が観測された（Figure 13）。

Scheme 9



Reagents and conditions: (a) TFAA, pyridine, DMAP, $CHCl_3$, rt, 89%; (b) $ClSO_3H$, $CHCl_3$, rt, 59% for **17**, 14% for **18**; (c) **45**, pyridine, DMAP, $CHCl_3$, rt, 95%; (d) KOH aq., EtOH, rt, 96%; (e) (4-*tert*-butylphenyl)acetaldehyde, $NaBH(OAc)_3$, THF, rt; (f) 4M HCl/EtOAc, EtOAc, rt, 60% in two steps.

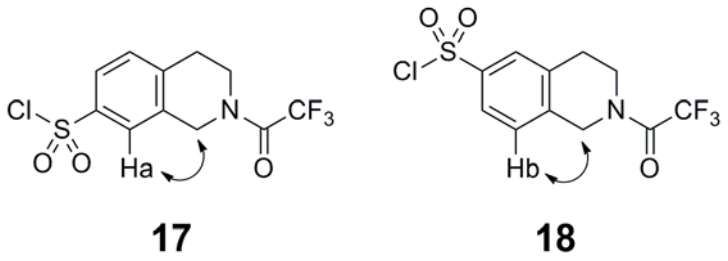
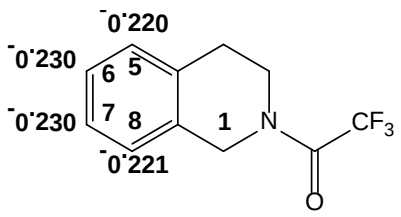


Figure 13. NOEs of compound **17** and **18**.

中間体 **16** に対するクロロスルホニル化反応における位置選択性を考察するために、中間体 **16** のベンゼン環上の電子密度計算を実施した。計算には Gaussian09 Revision D.01 プログラム [41]を用い、まず B3LYP/6-31G(d)[42]による中間体 **16** の構造最適化計算を行った。続いて B3LYP/6-31++G(d,p)による中間体 **16** の電子状態を計算し、Natural Population 解析 [43]により電子密度を算出した。その結果を Figure 14 に示したが、中間体 **16** の 6 位と 7 位の間に電子密度の有意な差は見られなかった。この結果から、単純に反応条件を最適化することでクロロスルホニル化反応の位置選択性をコントロールすることは困難であると判断した。



16

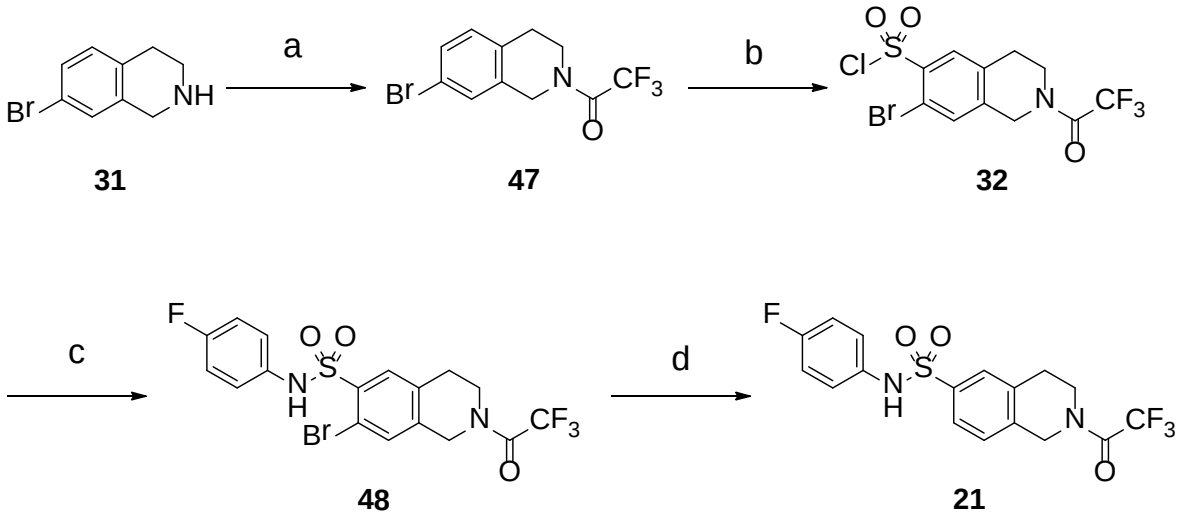
Figure 14. The electric density of compound **16**.

そこで、予め 7 位に置換基を導入して 6 位のみクロロスルホニル化反応を行った後に、7 位置換基を除去することで中間体 **46** を効率的に合成する戦略を考案した。すなわち、出発原料として化合物 **15** の代わりに、市販品であり、かつキログラム単位で入手可能な 7-bromo-1,2,3,4-tetrahydroisoqunoline（**31**）を選択し合成検討を行った。モデル反応として、スルホンアミド基窒素原子上の置換基に 4-fluoroaniline を用いて合成ルートを検討した（Scheme 10）。

出発原料 **31** をトリフルオロアセトアミド **47** に変換し、60 ℃ にてクロロスルホニル化反応を行ったところ、中間体 **32** が 72%の収率で得られることが分かった。この **32** と 4-fluoroaniline との縮合反応により高収率で目的物 **48** を得た（93% Yield）。**48** の水素添加による脱ブロモ化反応は円滑に進行し、98%の収率で目的化合物 **21** が得られた。こ

れらの結果から、出発原料を変更することで各工程とも問題なく進行することが分かった。

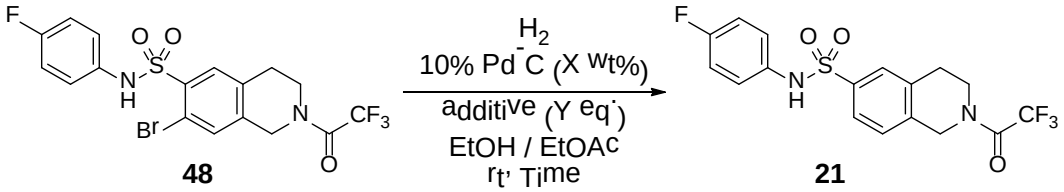
Scheme 10



Reagents and conditions: (a) TFAA, pyridine, DMAP, $CHCl_3$, rt, 96%; (b) $ClSO_3H$, $CHCl_3$, 60 °C, 72%; (c) 4-fluoroaniline, pyridine, DMAP, $CHCl_3$, rt, 93%; (d) H_2, 10% Pd-C (50 wt%), EtOH-EtOAc, rt, 98%.

しかしこの合成ルートは、水素添加による脱ブロモ化反応において基質に対して 50 wt%の Pd-C 触媒の量が必要であり、大量合成時の安全性や最終物の残留金属に関して課題となることが懸念された。従って、Pd-C 触媒の使用量低減化の検討を行った。その結果を Table 8 に示す。

Table 8. De-bromination by hydrogenolysis catalyzed by Pd-C



Entry	X wt%	additive (Y eq.)	Time (h)	Yield[a]
1	50	none	15	98%
2	10	none	15	63%[b]
3	10	Et_3N (1.2 eq.)	1	quant.

[a] Isolated yield.

[b] Determined by ^{1}H NMR.

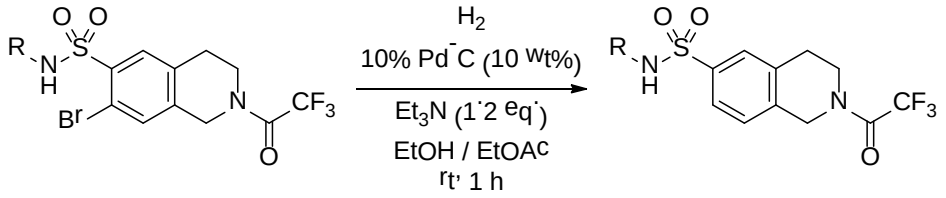
上述の通り、化合物 **48** の脱ブロモ化反応は 50 wt%量の Pd-C 触媒を用いると円滑に進行し、高収率で化合物 **21** が得られた（98% Yield、Entry 1）。一方、触媒量を 10 wt%まで低下させると反応が完結せずに収率が低下した（63% Yield、Entry 2）。

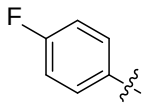
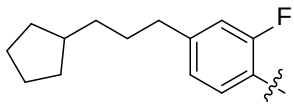
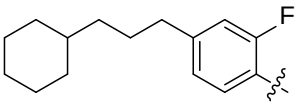
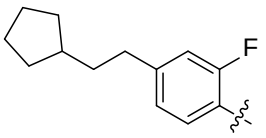
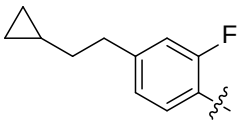
近年、佐治木らは、芳香族臭化物やヨウ化物と比べて反応性の低い芳香族塩化物の Pd-C 触媒存在下水素添加による脱クロロ化反応において、トリエチルアミンを共存することで反応が円滑に進行することを見出している[44]。そこで、脱ブロモ化反応においてもこの反応条件が適応できるかどうか検討を行った。すなわち、添加剤として Et_3N を用いて反応を行ったところ 、10 wt%の Pd 触媒量でも化合物 **48** の脱ブロモ化反応が速やかに進行し、化合物 **21** を高収率で与えることが明らかとなった（Entry 3）。本反応は、添加した Et_3N から Pd で活性化された芳香環に一電子移動が起こり、ラジカルアニオンが生成することによって反応が加速されていると推察されている[44]。

この反応条件を他のテトラヒドロイソキノリン誘導体の脱ブロモ化反応に適用した（Table 9）。いずれの基質においても円滑に反応が進行し、対応する目的物を高収率で

与える結果となった。Entry 2 に示すように、化合物 **39**（**TP0455353**）の置換基を有する化合物の脱ブロモ化反応においても目的物 **46** を 89%の収率で得ることができた。

Table 9. Reduction reaction of bromine substitution using triethylamine



Entry	R	Product Number	Yield (%)[a]
1		**21**	quant.
2		**46**	89
3		**49**	quant.
4		**50**	98
5		**51**	97

[a] Isolated yield.

水素添加による脱ブロモ化反応において、トリエチルアミンを添加することで反応時間を大幅に短縮し、用いる Pd-C 触媒の使用量を 1/5 まで低減化することに成功した。このことは、化合物 **39**（**TP0455353**）の合成において、収率および安全性の面からスケールアップに適用できることを示している（第２節で後述）。

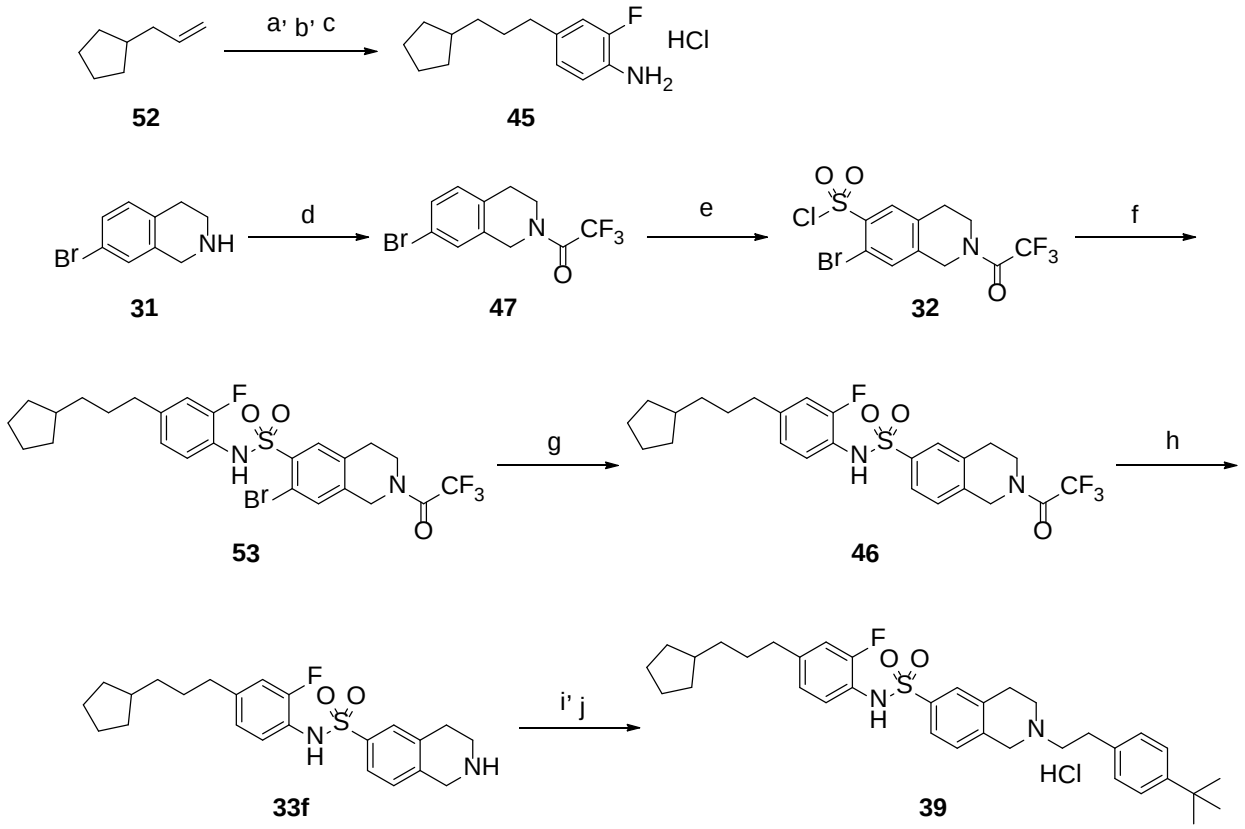
第２節　化合物 **39**（**TP0455353**）のスケールアップ合成

第 1 節で述べた最適化した反応条件を用いて、化合物 **39**（**TP0455353**）の 100 g スケールの合成を行った（Scheme 11）。用いるアニリン **45** は allylcyclopentane（**52**）より 3 工程により合成した。

100 g の 7-bromo-1,2,3,4-tetrahydroisoquinoline（**31**）に対し、無水トリフルオロ酢酸を用いて 2 級アミンを保護し化合物 **47** に変換した。化合物 **47** のクロロスルホニル化反応を行い、酢酸エチルとジイソプロピルエーテルからの結晶化により 110 g の中間体 **32** を得た後に、化合物 **45** と中間体 **32** との縮合反応を行い粗生成物 **53** を得た。トリエチルアミン存在下脱ブロモ化反応を行い、高収率で中間体 **46** を得た（2 工程、97%）。この中間体 **46** はシリカゲルクロマトグラフィーにより精製した。

塩基性条件下、中間体 **46** のトリフルオロアセチル基を除去して定量的に中間体 **33f** に変換し、(4-*tert*-butylphenyl)acetaldehyde との還元的アミノ化反応を行うことで、84.5 g の化合物 **39**（**TP0455353**）を合成した。出発原料 **31** から化合物 **39**（**TP0455353**）の総収率は 7 工程で 45%であり、最初の合成ルート（総収率：6.8%）より約 7 倍収率が向上した。

Scheme 11



Reagents and conditions: (a) 9-BBN, THF, rt; (b) **26**, $PdCl_2$(dppf), NaOH aq., THF, reflux; (c) 4M HCl/EtOAc, EtOAc, rt, 64% in three steps; (d) TFAA, pyridine, DMAP, $CHCl_3$, rt, 98%; (e) $ClSO_3H$, $CHCl_3$, 60 °C, 60%; (f) **45**, pyridine, $CHCl_3$, rt; (g) H_2, 10% Pd-C (50 wt%), EtOH-EtOAc, rt, 97% in two steps; (h) KOH aq., EtOH, rt, quant.; (i) (4-*tert*-butylphenyl)acetaldehyde, $NaBH(OAc)_3$, $CHCl_3$, rt; (j) 4M HCl/EtOAc, EtOAc, rt, 79% in two steps.

第３節　小括

強力な MGAT2 阻害活性を有する化合物 **39**（**TP0455353**）の合成法について検討を行った。出発原料としてテトラヒドロイソキノリンを用いていたが、クロロスルホニル化反応の選択性が低く、芳香環の電子密度計算から選択性の向上は困難であると判断した。そこで、出発原料を 7-bromo-1,2,3,4-tetrahydroisoquinoline（**31**）に変更し、効率的に 6 位クロロスルホニル体を合成する検討を行ったところ、各工程とも高収率で目的物を得ることができた。また、脱ブロモ化反応での触媒量低減を目的とした検討では、添加剤としてトリエチルアミンを用いることで触媒量を 1/5 に低減し、かつ高い基質一般性を持って目的物を得ることに成功した。これらの合成法検討により、出発原料 100 g から合成を行い 7 工程で 84.5 g の化合物 **39**（**TP0455353**）の合成を達成した。

結論

生体内脂肪合成酵素の一つである MGAT2 を阻害することで、小腸上皮細胞内での脂肪の再合成過程を阻害して脂肪吸収を抑制するという作用機序に基づく新規経口抗肥満薬の創出を目的として本研究を行った。

第 1 章では、HTS ヒット化合物 **1** の合成展開として、酵素阻害活性の向上と溶解度の改善にフォーカスし、スルホンアミド窒素に置換するベンゼン環上の置換基効果およびイソインドリン構造やリンカー部位の変換の構造活性相関について述べた。化合物 **1** のスルホンアミド基のベンゼン環上の置換基変換を行い、酵素阻害活性の向上したイソインドリン誘導体 **7e**（IC_{50} = 168 nM）を見出した。しかしながら、化合物 **1** と比べて化合物 **7e** の溶解度は向上したが（0.607 μg/mL in water）、マウス薬物動態試験における血中曝露量は極めて低い結果となった（Cmax = 94.3 ng/mL, $AUC_{0\text{-}4h}$ = 134 ng•h/mL）。一方、化合物 **1** のイソインドリン部位およびリンカー部位を変換した化合物 **22** は、酵素阻害活性は減弱するものの（IC_{50} = 1522 nM）、溶解度が **7e** と比較して約 1000 倍向上する結果を与えた（641 μg/mL in water）。溶解度向上によりマウス血中曝露量が向上し（C_{max} = 1200 ng/mL, $AUC_{0\text{-}4h}$ = 1808 ng•h/mL）、化合物 **22** が 100 mg/kg の用量で有意な脂肪吸収抑制作用を示すことを明らかにした。

第 2 章では、化合物 **22** のスルホンアミド窒素に置換するベンゼン環のパラ位置換基の最適化検討を行い、MGAT2 阻害活性の向上した化合物 **37**、**39** および **44c** を見出した。これら化合物の溶解度や肝代謝安定性などの in vitro 試験、マウス血中曝露量測定および in vivo 薬効試験を行った。その結果、FeSSIF に対する溶解度が高いほど、マウス血中曝露量が増加することを明らかにした。また、これらの化合物は in vivo マウス脂肪

負荷試験において、30 mg/kg の用量で有意な脂肪吸収抑制効果を示した。中でも強力な MGAT2 阻害活性を有する化合物 **39**（**TP0455353**）は 3 mg/kg の用量から in vivo 薬効を示すことを明らかにした。

第 3 章では、化合物 **39**（**TP0455353**）の大量合成を指向した合成法検討について述べた。テトラヒドロイソキノリンを出発原料とした初期合成法では、クロロスルホニル化反応における位置選択性が低いため、総収率が 6 工程で 6.8%と極めて低いものであった。そこで、出発原料として 7-bromo-1,2,3,4-tetrahydroisoquinoline を用いて検討を行ったところ、各工程とも良好な収率で反応が進行し、効率的に 6 位クロロスルホニル体を合成した。また、本合成ルートは脱ブロモ化反応における Pd-C の使用量が多いことが課題であったが、添加剤としてトリエチルアミンを用いることで反応が円滑に進行し、高い基質一般性を持って目的物が得られることを明らかとした。これらの合成法検討結果から、100 g スケールでの合成を達成し、84.5 g の化合物 **39**（**TP0455353**）を得ることに成功した（7 工程、総収率 45%）。

筆者は HTS ヒット化合物である化合物 **1** から MGAT2 阻害活性の構造活性相関を明らかにし、また、化合物の溶解度を向上させることで経口活性を有する新規 MGAT2 阻害剤 **39**（**TP0455353**）を創出した。強力な MGAT2 阻害活性を有する化合物 **39**（**TP0455353**）によって脂肪の再合成過程が阻害され、脂肪吸収を抑制するという作用機序を示すことができた。すなわち、in vitro での MGAT2 阻害活性向上と溶解度改善による経口吸収性向上を同時に実現する化合物を見出したことで、in vivo において低用量から強力な脂肪吸収抑制を示すことを明らかとした。このことは、KO マウスで観測された脂肪吸収抑制作用を阻害剤でも実証し、MGAT2 が抗肥満症薬の有用な標的分子であることを示したと言える。

謝辞

本論文を作成するにあたり、終始御懇篤な御指導と御鞭撻を賜りました東北大学大学院薬学研究科教授　岩渕好治先生に深甚なる謝意を表します。また、本論文の審査にあたり、有益な御助言と御高閲を賜りました東北大学大学院薬学研究科教授　根東義則先生、並びに東北大学大学院薬学研究科教授　徳山英利先生に深謝致します。

本研究の機会および本論文発表の許可を与えて頂きました大正製薬株式会社社長上原茂氏、同医薬研究本部本部長　奥山茂博士、同医薬研究本部副本部長　ロドニー W. スティーブンス博士、同化学研究所所長　大嶽憲一博士に厚く御礼申し上げます。

また、本論文を纏めるにあたり、終始御懇切なる御指導と御教示を戴きました大正製薬株式会社化学第 1 研究室室長　吉住隆博士に心より感謝申し上げます。

本研究を遂行するにあたり、終始御懇切なる御指導と御協力を頂きました大正製薬株式会社化学第 1 研究室　岡裕輔博士、河口尚則博士、岩切佳那子氏、同化学第 2 研究室田中宏明氏、宇根内史氏、同プロセス化学研究室　須賀洋一郎氏、大井隆宏氏、同研究推進室　高橋正人博士、同薬理第 2 研究室　宗友栄ニ氏、井尾房代氏、同薬理第 3 研究室　益子愛子氏、同安全性研究室　北野清和氏、同上原記念生命科学財団　斉藤雅子氏、同薬物動態研究室　皆川俊哉博士、神夏磯俊介氏、同医薬安全管理部　加藤幸司博士、同製剤研究室　吉田浩二氏、大崎尚人氏、野副晶子氏、同化学資源研究室　樋口彰氏、岡田敦司博士、関根寿代氏、徳良誠健博士、並びに佐藤長明博士、白崎仁久博士に深く御礼申し上げます。

最後に、本論文の作成にあたり常に支えとなってくれた妻　真由美をはじめ、家族に感謝致します。

実験の部

All commercially available starting materials and reagents were used without further purification unless otherwise noted. Thin layer chromatography was performed to monitor the reactions using Merck silica gel 60 F254 plates or Fuji Silysia chromatorex NH plates. Silica gel column chromatography was performed using Wakogel® C–200, or NH–silica gel Fuji Silysia chromatorex® DM1020, or an appropriately sized pre-packed silica cartridge on a Biotage system. Melting points were determined using a Yanako micro melting point apparatus and were not corrected. The ^{1}H NMR spectra were determined with a Varian Instruments INOVA300 spectrometer at 300 MHz or a JEOL ECA600 NMR spectrometer operating at 600 MHz. The ^{13}C NMR spectra were determined with a JEOL ECA600 NMR spectrometer operating at 151 MHz or a JEOL JNM-ECA500 NMR spectrometer operating at 126 MHz. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) as an internal reference. Multiplicity was defined as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), br s (broad singlet). IR spectra were recorded using a Perkin-Elmer Spectrum One. The mass spectra (MS) were recorded using a Shimadzu LCMS-2010EV mass spectrometer with an ESI/APCI dual source. HRMS were recorded using a Shimadzu LCMS-IT-TOF mass spectrometer with an ESI/APCI dual source or a Micromass GCT mass spectrometer with EI. Elemental analyses were performed using a Perkin–Elmer 2400II, and the results were within ±0.4% of the calculated values. The preparative HPLC purification condition was as follows: Gilson preparative HPLC system; column waters ODS sunfire, 50 mm x 30 mm; eluent A, water + 0.1% TFA; eluent B, acetonitrile + 0.1% TFA; 10% B up to 95% B in 12 min; Flow rate 40 mL/min.

1-(1,3-Dihydro-2*H*-isoindol-2-yl)-2,2,2-trifluoroethanone (3)[45)]

Pyridine (6.56 mL, 81.1 mmol) and DMAP (248 mg, 2.03 mmol) were added to a solution of 2,3-dihydro-1*H*-isoindole **2** (8.08 g, 40.6 mmol) in $CHCl_3$ (120 mL) at room temperature. The mixture was cooled to 0 °C, and TFAA (6.77 mL, 48.7 mmol) was added dropwise to the mixture. After the addition, the reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The mixture was then washed with 1 mol/L hydrochloric acid, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **3** (8.66 g, 99%) as a light brown powder: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.93 (s, 2 H), 5.04 (s, 2 H), 7.22–7.43 (m, 4 H); MS (ESI/APCI Dual): *m/z* 216 $[M+H]^+$.

2-(Trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonyl chloride (4)

A solution of **3** (5.00 g, 23.2 mmol) in $CHCl_3$ (80 mL) was cooled at –78 °C, and chlorosulfonic acid (10.1 mL, 152 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into an ice water. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **4** (5.15 g, 71%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.04 (s, 2 H), 5.16 (s, 2 H), 7.53–7.65 (m, 1 H), 7.93–8.09 (m, 2 H).

***N*-(4-Fluorophenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5a)**

Pyridine (2.57 mL, 31.9 mmol) and DMAP (195 mg, 1.59 mmol) were added to a solution of 4-fluoroaniline (1.86 g, 16.7 mmol) in $CHCl_3$ (46 mL) at room temperature. The mixture was cooled to 0 °C, and **4** (5.00 g, 15.9 mmol) was added to the mixture. The reaction mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The mixture was washed with 1 mol/L hydrochloric acid, and then brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. To the resulting residue was added Et_2O, and the resulting powder was collected by filtration to afford **5a** (5.85 g, 95%) as a pale pink powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.86 (s, 2 H), 5.06 (s, 2 H), 7.04–7.14 (m, 4 H), 7.47–7.59 (m, 1 H), 7.64–7.72 (m, 1 H), 7.75–7.82 (m, 1 H), 10.31 (br s, 1 H); MS (ESI/APCI Dual): *m/z* 387 $[M-H]^-$.

Compounds **5b** to **5j** were prepared from the corresponding anilines in the same procedure described for **5a**.

***N*-(2,4-Difluorophenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5b)**

Colorless powder (yield 34%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.81–4.93 (m, 2 H), 5.03–5.13 (m, 2 H), 6.98–7.07 (m, 1 H), 7.18–7.29 (m, 2 H), 7.52–7.61 (m, 1 H), 7.63–7.71 (m, 1 H), 7.73–7.78 (m, 1 H), 10.20 (s, 1 H); MS (ESI/APCI Dual): *m/z* 405 $[M-H]^-$.

***N*-(2-Chloro-4-fluorophenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5c)**

Colorless amorphous (yield 87%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88–5.09 (m, 4 H), 6.79 (s, 1 H), 6.97–7.07 (m, 2 H), 7.31–7.44 (m, 1 H), 7.63–7.74 (m, 3 H); MS (ESI/APCI Dual): *m/z* 421 $[M-H]^-$.

***N*-(2-Ethyl-4-fluorophenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5d)**

Pale yellow amorphous (yield 65%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.6 Hz, 3 H), 2.40 (q, *J* = 7.6 Hz, 2 H), 4.90–5.14 (m, 4 H), 6.18 (s, 1 H), 6.79–6.92 (m, 2 H), 7.12–7.18 (m, 1 H), 7.35–7.46 (m, 1 H), 7.63–7.74 (m, 2 H); MS (ESI/APCI Dual): *m/z* 415 $[M-H]^-$.

***N*-(4-Fluoro-2-methoxyphenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5e)**

Colorless amorphous (yield 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (s, 3 H), 4.87–5.08 (m, 4 H), 6.46–6.53 (m, 1 H), 6.59–6.69 (m, 1 H), 6.80 (s, 1 H), 7.29–7.42 (m, 1 H), 7.45–7.53 (m, 1 H), 7.65–7.76 (m, 2 H); MS (ESI/APCI Dual): *m/z* 417 $[M-H]^-$.

***N*-(2-Ethoxy-4-fluorophenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5f)**

Colorless amorphous (yield 91%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–1.30 (m, 3 H), 3.82 (q, *J* = 6.9 Hz, 2 H), 4.86–5.07 (m, 4 H), 6.42–6.49 (m, 1 H), 6.59–6.67 (m, 1 H), 6.78–6.82 (m, 1 H), 7.29–7.41 (m, 1 H), 7.46–7.54 (m, 1 H), 7.62–7.74 (m, 2 H); MS (ESI/APCI Dual): *m/z* 431 $[M-H]^-$.

***N*-(4-Fluoro-2-propoxyphenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5g)**

Colorless amorphous (yield 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.4 Hz, 3 H), 1.60–1.73 (m, 2 H), 3.71 (t, *J* = 6.6 Hz, 2 H), 4.86–5.06 (m, 4 H), 6.44–6.50 (m, 1 H), 6.59–6.67 (m, 1 H), 6.76–6.80 (m, 1 H), 7.29–7.39 (m, 1 H), 7.47–7.55 (m, 1 H), 7.63–7.73 (m, 2 H); MS (ESI/APCI Dual): *m/z* 445 $[M-H]^-$.

***N*-(2,4-Dimethoxyphenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5h)**

Colorless amorphous (yield 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3 H), 3.76 (s, 3 H), 4.85–5.06 (m, 4 H), 6.27–6.32 (m, 1 H), 6.41–6.48 (m, 1 H), 6.67 (s, 1 H), 7.28–7.39 (m, 1 H), 7.41–7.48 (m, 1 H), 7.62–7.74 (m, 2 H); MS (ESI/APCI Dual): *m/z* 429 $[M-H]^-$.

***N*-(2-Fluoro-4-methoxyphenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5i)**

Pale pink powder (yield 87%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3 H), 4.84–5.14 (m, 4 H), 6.37 (s, 1 H), 6.46–6.56 (m, 1 H), 6.65–6.76 (m, 1 H), 7.30–7.55 (m, 2 H), 7.63–7.74 (m, 2 H); MS (ESI/APCI Dual): *m/z* 417 $[M-H]^-$.

***N*-[2-Fluoro-4-(pentyloxy)phenyl]-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (5j)**

Colorless amorphous (yield 84%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88–0.95 (m, 3 H), 1.33–1.44 (m, 4 H), 1.69–1.82 (m, 2 H), 3.88 (t, *J* = 6.5 Hz, 2 H), 4.87–5.09 (m, 4 H), 6.34 (s, 1 H), 6.44–6.53 (m, 1 H), 6.63–6.70 (m, 1 H), 7.30–7.51 (m, 2 H), 7.62–7.72 (m, 2 H); MS (ESI/APCI Dual): *m/z* 473 $[M-H]^-$.

***N*-(4-Fluorophenyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (6a)**

A solution of potassium hydroxide (1.69 g, 30.1 mmol) in water (30 mL) was added to a solution of **5a** (5.85 g, 15.1 mmol) in EtOH (120 mL) at room temperature, and the reaction mixture was stirred for 3 h. After the reaction mixture was concentrated by distillation under reduced pressure, and the residue was diluted with water. The resulting mixture was acidified by addition of 3 mol/L hydrochloric acid, and then neutralized by addition of saturated aqueous $NaHCO_3$. The mixture was extracted three times with 10% MeOH/$CHCl_3$. The combined

organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. To the residue was added 50% EtOAc/*n*-hexane, and the resulting precipitates were collected by filtration to afford crude **6a** (4.09 g, 93%) as a pale yellow powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.18 (s, 3 H), 7.05–7.11 (m, 4 H), 7.41–7.47 (m, 1 H), 7.55–7.61 (m, 1 H), 7.64–7.67 (m, 1 H); MS (ESI/APCI Dual): *m/z* 293 $[M+H]^+$, 291 $[M-H]^-$.

***N*-(4-*tert*-Butylphenyl)-5-[(4-fluorophenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (1)**

Potassium hydroxide (286 mg, 5.10 mmol) was added to a solution of **5a** (990 mg, 2.55 mmol) in 20% water/EtOH (13 mL) at room temperature, and the mixture was stirred overnight. The reaction mixture was distilled off under reduced pressure, and water was added to the residue. The mixture was neutralized by addition of 1 mol/L hydrochloric acid, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **6a** (615 mg) as a purple amorphous.

To a solution of crude **6a** (200 mg) in 10% $CHCl_3$/DMSO (3.5 mL) were added triethylamine (95.4 µL, 0.684 mmol) and 4-*tert*-butylphenyl isocyanate (122 µL, 0.684 mmol) at room temperature, and the reaction mixture was stirred for 2 h. The reaction was quenched by addition of 1 mol/L hydrochloric acid, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 33% EtOAc/*n*-hexane and then 10% MeOH/$CHCl_3$. The fractions including compound **1** were collected and evaporated by rotary evaporation. To the residue was added EtOAc, and the resulting precipitates were collected by filtration to afford **1** (124 mg, 32%) as a colorless powder: mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 4.77 (s, 4

H), 7.07–7.12 (m, 4 H), 7.23–7.30 (m, 2 H), 7.41–7.47 (m, 2 H), 7.49–7.55 (m, 1 H), 7.61–7.67 (m, 1 H), 7.70 (s, 1 H), 8.30 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 115.8, 116.0, 119.4, 121.3, 122.8, 122.9, 123.7, 124.9, 125.9, 133.9, 137.6, 138.3, 138.6, 142.3, 144.1, 154.0, 158.3, 159.9; IR (KBr): 3394, 3056, 1641, 1529, 1505, 1304, 1154 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{25}H_{26}FN_3O_3S$ $[M+H]^+$, 468.1752. Found: 468.1757.

Compounds **7b** to **7j** were prepared from the corresponding starting materials in the same procedure described for **1**.

***N*-(4-*tert*-Butylphenyl)-5-[(2,4-difluorophenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (7b)**

Colorless powder (yield 45%): mp 232–234 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 4.73–4.85 (m, 4 H), 6.98–7.09 (m, 1 H), 7.18–7.31 (m, 4 H), 7.41–7.48 (m, 2 H), 7.50–7.57 (m, 1 H), 7.60–7.70 (m, 2 H), 8.31 (s, 1 H), 10.14 (s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 104.5, 104.7, 104.9, 111.6, 111.7, 111.8, 119.4, 121.2, 123.7, 124.9, 125.9, 128.8, 128.9, 137.6, 138.2, 139.2, 142.3, 144.2, 154.0, 155.5, 157.5, 159.1, 161.0; IR (KBr): 3399, 2968, 1642, 1532, 1511, 1309, 1154 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{25}H_{25}F_2N_3O_3S$ $[M+H]^+$, 486.1657. Found: 486.1657.

***N*-(4-*tert*-Butylphenyl)-5-[(2-chloro-4-fluorophenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (7c)**

Colorless powder (yield 64%): mp 207–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 4.75–4.84 (m, 4 H), 7.14–7.31 (m, 4 H), 7.40–7.48 (m, 3 H), 7.51–7.57 (m, 1 H), 7.60–7.69 (m, 2 H), 8.32 (s, 1 H), 10.1 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 114.9, 115.0, 117.1, 117.2, 119.4, 121.3, 123.7, 124.9, 126.0, 129.8, 137.6, 138.2, 139.5, 142.2, 144.1, 154.0, 159.1, 160.7; IR (KBr): 3395, 2965, 1655, 1519, 1337, 1151 cm^{-1}; MS (ESI/APCI

Dual): *m/z* 502 $[M+H]^+$, 500 $[M-H]^-$; Anal. Calcd for $C_{25}H_{25}ClFN_3O_3S$: C, 59.81; H, 5.02; N, 8.37. Found: C, 59.79; H, 5.01; N, 8.32.

_N_-(4-*tert*-Butylphenyl)-5-[(2-ethyl-4-fluorophenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (7d)

Colorless powder (yield 61%): mp 229–231 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (t, *J* = 7.5 Hz, 3 H), 1.26 (s, 9 H), 3.26–3.39 (m, 2 H), 4.75–4.84 (m, 4 H), 6.80–6.93 (m, 2 H), 7.02–7.08 (m, 1 H), 7.24–7.30 (m, 2 H), 7.42–7.47 (m, 2 H), 7.52–7.56 (m, 1 H), 7.59–7.63 (m, 2 H), 8.32 (s, 1 H), 9.60 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 14.0, 23.3, 31.3, 33.9, 51.7, 51.8, 112.9, 113.0, 115.3, 115.5, 119.5, 121.3, 123.7, 124.9, 126.0, 129.1, 129.1, 130.2, 137.6, 138.2, 139.6, 142.0, 144.0, 144.0, 144.1, 154.0, 159.9, 161.5; IR (KBr): 3378, 2964, 1654, 1330, 1530, 1413, 1330, 1151 cm^{-1}; MS (ESI/APCI Dual): *m/z* 496 $[M+H]^+$, 494 $[M-H]^-$; Anal. Calcd for $C_{27}H_{30}FN_3O_3S$: C, 65.43; H, 6.10; N, 8.48. Found: C, 65.23; H, 6.08; N, 8.38.

_N_-(4-*tert*-Butylphenyl)-5-[(4-fluoro-2-methoxyphenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (7e)

Colorless powder (yield 60%): mp 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 3.46 (s, 3 H), 4.74–4.82 (m, 4 H), 6.64–6.75 (m, 1 H), 6.78–6.88 (m, 1 H), 7.14–7.22 (m, 1 H), 7.23–7.30 (m, 2 H), 7.41–7.51 (m, 3 H), 7.56–7.66 (m, 2 H), 8.31 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 55.8, 100.1, 100.3, 106.4, 106.6, 119.4, 121.2, 121.3, 123.2, 124.9, 126.0, 127.8, 127.9, 137.6, 137.8, 139.8, 141.8, 144.1, 154.0, 154.5, 154.5, 160.1, 161.7; IR (KBr): 3378, 2951, 1651, 1528, 1501, 1326, 1152 cm^{-1}; MS (ESI/APCI Dual): *m/z* 498 $[M+H]^+$, 496 $[M-H]^-$; Anal. Calcd for $C_{26}H_{28}FN_3O_4S$: C, 62.76; H, 5.67; N, 8.44. Found: C, 62.56; H, 5.70; N, 8.37.

_N_-(4-_tert_-Butylphenyl)-5-[(2-ethoxy-4-fluorophenyl)sulfamoyl]-1,3-dihydro-2_H_-isoindole-2-carboxamide (7f)

Colorless powder (yield 36%): mp 196–198 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07 (t, J = 6.9 Hz, 3 H), 1.26 (s, 9 H), 3.73 (q, J = 6.9 Hz, 2 H), 4.67–4.84 (m, 4 H), 6.65–6.84 (m, 2 H), 7.18–7.31 (m, 3 H), 7.40–7.51 (m, 3 H), 7.55–7.64 (m, 2 H), 8.31 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 13.9, 31.3, 33.9, 51.6, 51.8, 64.0, 100.5, 100.6, 106.2, 106.4, 119.4, 121.2, 121.3, 123.2, 124.9, 126.0, 128.0, 128.1, 137.6, 137.7, 139.8, 141.8, 144.1, 153.5, 153.6, 154.0, 160.1, 161.7; IR (KBr): 3362, 2965, 1647, 1537, 1506, 1338, 1154 cm^{-1}; MS (ESI/APCI Dual): *m/z* 512 $[M+H]^+$, 510 $[M-H]^-$; Anal. Calcd for $C_{27}H_{30}FN_3O_4S$: C, 63.39; H, 5.91; N, 8.21. Found: C, 63.32; H, 5.93; N, 8.19.

_N_-(4-_tert_-Butylphenyl)-5-[(4-fluoro-2-propoxyphenyl)sulfamoyl]-1,3-dihydro-2_H_-isoindole-2-carboxamide (7g)

Colorless powder (yield 37%): mp 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.82 (t, J = 7.5 Hz, 3 H), 1.26 (s, 9 H), 1.37–1.53 (m, 2 H), 3.62 (t, J = 6.6 Hz, 2 H), 4.71–4.82 (m, 4 H), 6.64–6.75 (m, 1 H), 6.77–6.85 (m, 1 H), 7.18–7.30 (m, 3 H), 7.40–7.51 (m, 3 H), 7.53–7.63 (m, 2 H), 8.31 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 10.2, 21.5, 31.3, 33.9, 51.7, 51.8, 69.9, 100.5, 100.7, 106.2, 106.3, 119.4, 121.1, 121.2, 123.2, 124.9, 125.9, 128.0, 128.0, 137.6, 137.8, 139.9, 141.8, 144.1, 153.8, 154.0, 160.1, 161.7; IR (KBr): 3371, 2964, 1653, 1531, 1506, 1336, 1155 cm^{-1}; MS (ESI/APCI Dual): *m/z* 526 $[M+H]^+$, 524 $[M-H]^-$; Anal. Calcd for $C_{28}H_{32}FN_3O_4S$: C, 63.98; H, 6.14; N, 7.99. Found: C, 63.91; H, 6.11; N, 7.97.

_N_-(4-_tert_-Butylphenyl)-5-[(2,4-dimethoxyphenyl)sulfamoyl]-1,3-dihydro-2_H_-isoindole-2-carboxamide (7h)

Colorless powder (yield 69%): mp 176–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9

H), 3.40 (s, 3 H), 3.71 (s, 3 H), 4.74–4.82 (m, 4 H), 6.42–6.49 (m, 2 H), 7.04–7.11 (m, 1 H), 7.23–7.31 (m, 2 H), 7.41–7.51 (m, 3 H), 7.53–7.63 (m, 2 H), 8.31 (s, 1 H), 9.28 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 55.3, 98.9, 104.6, 117.7, 119.4, 121.3, 123.0, 124.9, 126.1, 128.3, 137.6, 137.6, 140.1, 141.5, 144.1, 154.0, 154.6, 158.8; IR (KBr): 3363, 2960, 1643, 1537, 1509, 1334, 1150 cm^{-1}; MS (ESI/APCI Dual): *m/z* 510 $[M+H]^+$, 508 $[M-H]^-$; Anal. Calcd for $C_{27}H_{31}N_3O_5S$: C, 63.63; H, 6.13; N, 8.25. Found: C, 63.55; H, 6.10; N, 8.11.

_N_-(4-*tert*-Butylphenyl)-5-[(2-fluoro-4-methoxyphenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (7i)

Colorless powder (yield 84%): mp 200–202 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 3.71 (s, 3 H), 4.75–4.83 (m, 4 H), 6.66–6.72 (m, 1 H), 6.76–6.83 (m, 1 H), 7.03–7.09 (m, 1 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 7.49–7.55 (m, 1 H), 7.59–7.66 (m, 2 H), 8.32 (s, 1 H), 9.85 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.3, 33.9, 51.7, 51.8, 55.7, 102.0, 102.1, 110.3, 119.4, 121.2, 123.5, 124.9, 126.0, 129.2, 137.6, 138.0, 139.4, 142.0, 144.1, 154.0, 156.6, 158.8; IR (KBr): 3393, 2958, 1655, 1515, 1338, 1151 cm^{-1}; MS (ESI/APCI Dual): *m/z* 498 $[M+H]^+$, 496 $[M-H]^-$; Anal. Calcd for $C_{26}H_{28}FN_3O_4S$: C, 62.76; H, 5.67; N, 8.44. Found: C, 62.55; H, 5.72; N, 8.32.

_N_-(4-*tert*-Butylphenyl)-5-{[2-fluoro-4-(pentyloxy)phenyl]sulfamoyl}-1,3-dihydro-2*H*-isoindole-2-carboxamide (7j)

Colorless powder (yield 65%): mp 145–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.82–0.92 (m, 3 H), 1.26 (s, 9 H), 1.28–1.39 (m, 4 H), 1.60–1.73 (m, 2 H), 3.90 (t, *J* = 6.5 Hz, 2 H), 4.74–4.85 (m, 4 H), 6.65–6.72 (m, 1 H), 6.74–6.82 (m, 1 H), 7.00–7.10 (m, 1 H), 7.24–7.32 (m, 2 H), 7.42–7.48 (m, 2 H), 7.50–7.55 (m, 1 H), 7.58–7.67 (m, 2 H), 8.31 (s, 1 H), 9.84 (br s, 1 H); ^{13}C

NMR (151 MHz, DMSO-d_6): δ 13.9, 21.8, 27.6, 28.1, 31.3, 33.9, 51.7, 51.8, 68.1, 102.3, 110.7, 119.4, 121.2, 123.5, 124.9, 126.0, 129.2, 137.6, 138.0, 139.5, 142.0, 144.1, 154.0, 156.6, 158.2; IR (KBr): 3394, 2958, 1657, 1512, 1339, 1151 cm^{-1}; MS (ESI/APCI Dual): *m/z* 554 $[M+H]^+$, 552 $[M-H]^-$; Anal. Calcd for $C_{30}H_{36}FN_3O_4S$: C, 65.08; H, 6.55; N, 7.59. Found: C, 65.04; H, 6.52; N, 7.47.

4-[(2,4-Dimethoxybenzyl)amino]-3-fluorophenol (9)

To a solution of 4-amino-3-fluorophenol **8** (5.00 g, 39.3 mmol) in THF (120 mL) were added acetic acid (16.2 mL, 283 mmol), 2,4-dimethoxybenzaldehyde (7.84 g, 47.2 mmol) and sodium triacetoxyborohydride (25.0 g, 118 mmol). The reaction mixture was stirred at room temperature for 5 h. After the volatiles were removed by rotary evaporation, saturated aqueous $NaHCO_3$ (500 mL) was added to the residue, and the mixture was extracted three times with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 30% to 45% EtOAc/*n*-hexane to afford **9** (12.0 g, 92%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3 H), 3.83 (s, 3 H), 4.22 (s, 2 H), 6.33–6.73 (m, 5 H), 7.16 (d, *J* = 8.1 Hz, 1 H); MS (ESI/APCI dual): *m/z* 276 $[M-H]^-$.

***N*-(2,4-Dimethoxybenzyl)-*N*-(2-fluoro-4-hydroxyphenyl)-2-(trifluoroacetyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (10)**

Compound **10** was prepared by the same procedure described for **5a** using compound **9** instead of 4-fluoroaniline.

Colorless powder (yield 52%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.56 (s, 3 H), 3.70 (s, 3 H), 4.56 (s, 2 H), 4.87–5.19 (m, 4 H), 6.37–6.53 (m, 4 H), 6.70–6.81 (m, 1 H), 7.04–7.12 (m, 1 H), 7.56–7.71 (m, 2 H), 7.74–7.83 (m, 1 H), 10.05 (s, 1 H).

***N*-(4-*tert*-Butylphenyl)-5-[(2,4-dimethoxybenzyl)(2-fluoro-4-hydroxyphenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (11)**

Compound **11** was prepared by the same procedure described for **1** using compound **10** instead of **5a**.

Colorless powder (yield 49%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 9 H), 3.56 (s, 3 H), 3.70 (s, 3 H), 4.56 (s, 2 H), 4.84 (d, *J* = 12 Hz, 4 H), 6.32–6.56 (m, 4 H), 6.69–6.80 (m, 1 H), 7.04–7.11 (m, 1 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 7.46 (d, *J* = 8.6 Hz, 2 H), 7.51–7.78 (m, 3 H), 8.35 (s, 1 H), 10.04 (br s, 1 H).

***N*-(4-*tert*-Butylphenyl)-5-[(4-ethoxy-2-fluorophenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (12a)**

To a solution of **11** (40.0 mg, 0.0631 mmol) in DMF (400 μL) were added iodoethane (7.69 μL, 0.0946 mmol) and potassium carbonate (17.0 mg, 0.126 mmol), and the mixture was stirred at room temperature for 3 days. To the reaction mixture was added water, and the mixture was extracted three times with EtOAc. The combined organic layers were concentrated under reduced pressure. After the resulting residue was dissolved in $CHCl_3$ (1.8 mL), TFA (0.2 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by preparative HPLC to afford **12a** (14.6 mg, 46%) as a colorless powder: ^{1}H NMR (600 MHz, DMSO- d_6): δ 1.26 (s, 9 H), 1.28 (t, *J* = 7.0 Hz, 2 H), 3.97 (d, *J* = 7.0 Hz, 3 H), 4.75–4.83 (m, 4 H), 6.66–6.71 (m, 1 H), 6.75–6.80 (m, 1 H), 7.01–7.08 (m, 1 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.50–7.54 (m, 1 H), 7.59–7.63 (m, 1 H), 7.64 (s, 1 H), 8.32 (s, 1 H), 9.83 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.4, 31.3, 33.9, 51.7, 51.8, 63.7, 102.3, 102.5, 110.6, 119.4, 121.2, 123.5, 124.9, 126.0, 129.2, 137.6, 138.0, 139.5, 142.0, 144.1, 154.0, 158.4; IR (KBr): 3365, 2963, 1642, 1514, 1323, 1145 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for

$C_{27}H_{30}FN_3O_4S$ $[M+H]^+$, 512.2014. Found: 512.2005.

Compounds **12b** and **12c** were prepared by the same procedure described for **12a** using 1-iodopropane and 1-iodobutane respectively instead of iodoethane.

***N*-(4-*tert*-Butylphenyl)-5-[(2-fluoro-4-propoxyphenyl)sulfamoyl]-1,3-dihydro-2*H*-isoindole-2-carboxamide (12b)**

Colorless powder (yield 55%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (t, J = 7.4 Hz, 3 H), 1.26 (s, 9 H), 1.62–1.75 (m, 2 H), 3.87 (t, J = 6.5 Hz, 2 H), 4.71–4.86 (m, 4 H), 6.65–6.83 (m, 2 H), 6.99–7.10 (m, 1 H), 7.27 (d, J = 8.7 Hz, 2 H), 7.44 (d, J = 8.7 Hz, 2 H), 7.50–7.56 (m, 1 H), 7.58–7.69 (m, 2 H), 8.31 (s, 1 H), 9.83 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 10.3, 21.8, 31.3, 33.9, 51.7, 51.8, 69.5, 102.3, 102.5, 110.7, 119.4, 121.2, 123.6, 124.9, 126.0, 129.2, 137.6, 138.0, 139.5, 142.0, 144.1, 154.0, 156.4, 158.4; IR (KBr): 3381, 2966, 1642, 1512, 1338, 1152 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{28}H_{32}FN_3O_4S$ $[M+H]^+$, 526.2170. Found: 526.2166.

5-[(4-Butoxy-2-fluorophenyl)sulfamoyl]-*N*-(4-*tert*-butylphenyl)-1,3-dihydro-2*H*-isoindole-2-carboxamide (12c)

Colorless powder (yield 68%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.90 (t, J = 7.4 Hz, 3 H), 1.26 (s, 9 H), 1.35–1.43 (m, 2 H), 1.61–1.68 (m, 2 H), 3.91 (t, J = 6.6 Hz, 2 H), 4.75–4.83 (m, 4 H), 6.65–6.72 (m, 1 H), 6.75–6.81 (m, 1 H), 7.00–7.08 (m, 1 H), 7.24–7.30 (m, 2 H), 7.42–7.47 (m, 2 H), 7.50–7.54 (m, 1 H), 7.60–7.63 (m, 1 H), 7.65 (s, 1 H), 8.32 (s, 1 H), 9.83 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.6, 18.6, 30.5, 31.3, 33.9, 51.7, 51.8, 67.8, 102.3, 102.5, 110.7, 119.4, 121.2, 123.6, 124.9, 126.0, 129.2, 137.6, 138.0, 142.0, 144.1, 154.0, 156.4, 158.4; IR (KBr): 3394, 2962, 1656, 1512, 1338, 1150 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{29}H_{34}FN_3O_4S$ $[M+H]^+$, 540.2327. Found: 540.2331.

2-[(4-*tert*-Butylphenyl)acetyl]-*N*-(4-fluorophenyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (13)

To a suspension of **6a** (190 mg, 0.650 mmol) in $CHCl_3$ (3 mL) were added (4-*tert*-butylphenyl)acetic acid (150 mg, 0.780 mmol), HOBt・H_2O (149 mg, 0.975 mmol), and EDC・HCl (187 mg, 0.975 mmol). The reaction mixture was stirred at room temperature overnight. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine and then saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 33% EtOAc/*n*-hexane and then 10% MeOH/$CHCl_3$. The fractions including compound **13** were collected and evaporated by rotary evaporation. To the residue was added EtOAc, and the resulting precipitates were collected by filtration to afford **13** (88.2 mg, 29%) as a colorless powder: mp 249–251 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23–1.29 (m, 9 H), 3.67 (s, 2 H), 4.67 (s, 2 H), 4.92 (s, 2 H), 7.04–7.11 (m, 4 H), 7.16–7.22 (m, 2 H), 7.29–7.36 (m, 2 H), 7.45–7.55 (m, 1 H), 7.58–7.67 (m, 1 H), 7.68–7.77 (m, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 31.2, 34.1, 51.6, 51.7, 51.8, 115.8, 116.0, 121.7, 122.7, 122.8, 122.8, 122.9, 123.7, 124.0, 125.0, 126.0, 129.0, 129.1, 132.1, 137.7, 138.2, 138.7, 141.6, 148.7, 169.3; IR (KBr): 2963, 1636, 1508, 1439, 1148 cm^{-1}; MS (ESI/APCI Dual): *m/z* 467 $[M+H]^+$, 465 $[M-H]^-$; Anal. Calcd for $C_{26}H_{27}FN_2O_3S$: C, 66.93; H, 5.83; N, 6.00. Found: C, 66.96; H, 5.80; N, 6.04.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(4-fluorophenyl)-2,3-dihydro-1*H*-isoindole-5-sulfonamide (14)

A borane-THF complex (0.9 mol/L THF solution, 0.538 mL, 0.484 mmol) was added to a solution of **13** (113 mg, 0.242 mmol) in THF (3 mL) at room temperature, and the mixture was heated at reflux temperature for 2 h. After cooling to room temperature, 6 mol/L hydrochloric acid (5 mL) was added, and the mixture was stirred at 90 °C for 1 h. The mixture was cooled to

0 °C, 6 mol/L aqueous sodium hydroxide was added to adjust the pH to 8 to 9, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 33% EtOAc/*n*-hexane to afford **14** (53.9 mg) as a colorless amorphous. To a solution of **14** in EtOAc (3 mL) was added 4 mol/L hydrogen chloride in EtOAc (0.5 mL), and the mixture was stirred at room temperature for 0.5 h. After the volatiles were removed by rotary evaporation, EtOAc/Et_2O was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **14** (38.2 mg, 30%) as a gray powder: mp 142–148 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.27 (s, 9 H), 2.95–3.02 (m, 2 H), 3.49–3.65 (m, 2 H), 4.51–4.70 (m, 2 H), 4.78–4.98 (m, 2 H), 7.04–7.15 (m, 4 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.53–7.62 (m, 1 H), 7.70–7.76 (m, 1 H), 7.79 (s, 1 H), 10.38 (s, 1 H), 11.32 (br s, 1 H); HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{26}H_{29}FN_2O_2S$ $[M+H]^+$, 453.2007. Found: 453.2001.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (16)[35)]

Pyridine (6.47 mL, 80.0 mmol) and DMAP (244 mg, 2.00 mmol) were added to a solution of 1,2,3,4-tetrahydroisoquinoline **15** (5.00 mL, 40 mmol) in $CHCl_3$ (100 mL) at room temperature. The mixture was cooled to 0 °C, and TFAA (6.67 mL, 48.0 mmol) was added in a dropwise manner to the mixture. After the addition, the reaction mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The mixture was then washed with 1 mol/L hydrochloric acid, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **16** (8.16 g, 89%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.92–2.98 (m, 2 H), 3.81–3.91 (m, 2 H), 4.71–4.82 (m, 2 H),

7.08–7.30 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.8, 29.1, 41.8, 43.3, 45.5, 46.9, 113.6, 115.5, 117.4, 119.4, 126.0, 126.5, 126.8, 126.9, 127.1, 127.5, 128.6, 128.8, 131.4, 133.2, 134.0, 155.9, 156.0; HRMS (EI): *m/z* Calcd for $C_{11}H_{10}F_3NO$ $[M]^+$, 229.0714. Found: 229.0701.

2-(Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride (17) and 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonyl chloride (18)[35)]

A solution of **16** (200 mg, 0.873 mmol) in $CHCl_3$ (3 mL) was cooled at 0 °C, and chlorosulfonic acid (379 μL, 5.70 mmol) was added in a dropwise manner. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into ice water. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 20% EtOAc/*n*-hexane to afford **17** (169 mg, 59%) and **18** (39.3 mg, 14%).

2-(Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride (17)

Colorless amorphous: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.04–3.13 (m, 2 H), 3.87–4.01 (m, 2 H), 4.83–4.94 (m, 2 H), 7.40–7.49 (m, 1 H), 7.80–7.95 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 28.2, 29.6, 40.9, 42.6, 45.2, 46.7, 115.3, 117.2, 124.8, 125.4, 125.4, 125.9, 130.2, 130.5, 133.4, 133.7, 141.5, 142.4, 142.9, 143.0; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{11}H_9ClF_3NO_3S$: $[M+Cl]^-$, 361.9638. Found: 361.9667.

2-(Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonyl chloride (18)

Colorless amorphous: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.06–3.14 (m, 2 H), 3.90–4.00 (m, 2 H), 4.85–4.94 (m, 2 H), 7.37–7.46 (m, 1 H), 7.85–7.94 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.9, 29.2, 41.0, 42.7, 45.4, 46.9, 115.3, 117.2, 125.3, 127.3, 127.6, 128.1, 135.4, 136.3, 139.2,

139.6, 143.1, 143.5; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{11}H_9ClF_3NO_3S$: $[M-H]^-$, 325.9871. Found: 325.9899.

***N*-(4-Fluorophenyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (19)**

Compound **19** was prepared by the same procedure described for **5a** using compound **17** instead of **4**.

Colorless amorphous (yield 92%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93–3.08 (m, 2 H), 3.80–3.96 (m, 2 H), 4.67–4.85 (m, 2 H), 6.52–6.71 (m, 1 H), 6.90–7.12 (m, 4 H), 7.20–7.33 (m, 1 H), 7.45–7.62 (m, 2 H); MS (ESI/APCI Dual): *m/z* 401 $[M-H]^-$.

***N*-(4-Fluorophenyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (21)**

Compound **21** was prepared by the same procedure described for **5a** using compound **18** instead of **4**.

Colorless amorphous (yield 92%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90–3.02 (m, 2 H), 3.80–3.95 (m, 2 H), 4.75–4.87 (m, 2 H), 6.63–6.74 (m, 1 H), 6.90–7.10 (m, 4 H), 7.18–7.29 (m, 1 H), 7.51–7.61 (m, 2 H); MS (ESI/APCI Dual): *m/z* 401 $[M-H]^-$.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (20)

A solution of potassium hydroxide (254 mg, 4.53 mmol) in water (2 mL) was added to a solution of **19** (1.22 g, 3.02 mmol) in EtOH (18 mL) at room temperature, and the reaction mixture was stirred for 14 h. A solution of potassium hydroxide (254 mg, 4.53 mmol) in water (2 mL) was added to the mixture, and the reaction mixture was stirred for 3 h. After the reaction mixture was concentrated by distillation under reduced pressure, and the residue was diluted with water. The resulting mixture was acidified by addition of 1 mol/L hydrochloric acid and

then neutralized by addition of saturated aqueous $NaHCO_3$. The resulting precipitates were collected by filtration to afford crude product (849 mg, 92%) as a colorless powder.

To a suspension of the crude product (153 mg, 0.500 mmol) in $CHCl_3$ (10 mL) were added (4-*tert*-butylphenyl)acetic acid (106 mg, 0.650 mmol), HOBt・H_2O (100 mg, 0.650 mmol) and EDC・HCl (125 mg, 0.650 mmol). The reaction mixture was stirred at room temperature for 15 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 25% to 60% EtOAc/*n*-hexane. The fractions including product were collected and evaporated by rotary evaporation. To the residue was added EtOAc/IPE/*n*-hexane, and the resulting precipitates were collected by filtration to afford the target intermediate (168 mg, 70%) as a colorless powder.

A borane-THF complex (0.9 mol/L THF solution, 0.770 mL, 0.696 mmol) was added to a solution of the above intermediate (167 mg, 0.348 mmol) in THF (8 mL) at 0 °C, and the mixture was heated at reflux temperature for 6 h. After cooling to room temperature, 6 mol/L hydrochloric acid (6 mL) was added, and the mixture was stirred at reflux temperature for 3 h. The mixture was cooled to 0 °C, 6 mol/L aqueous sodium hydroxide was added to adjust the pH to 8 to 9, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 0 to 5% MeOH/$CHCl_3$ to afford **20** (109 mg, 67%) as a colorless amorphous. To a solution of **20** in EtOAc (4 mL) was added 4 mol/L hydrogen chloride in EtOAc (1 mL), and the mixture was stirred at room temperature for 15 h. After the volatiles were removed by rotary evaporation, Et_2O was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **20** (97.8 mg, 83%) as a colorless powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (s, 9 H), 2.94–3.24 (m, 5 H), 3.34–3.50 (m, 2 H), 3.72–3.84 (m, 1 H), 4.33–4.48 (m, 1 H), 4.63–4.80 (m,

1 H), 7.07–7.15 (m, 4 H), 7.18–7.25 (m, 2 H), 7.34–7.40 (m, 2 H), 7.42–7.48 (m, 1 H), 7.59–7.68 (m, 2 H), 10.36 (s, 1 H), 10.65 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 25.0, 31.1, 34.2, 48.2, 51.0, 56.0, 115.8, 116.0, 122.6, 122.7, 125.1, 125.4, 125.5, 128.4, 129.7, 129.9, 133.8, 133.9, 137.0, 137.7, 149.2, 158.2, 159.8; IR (KBr): 2965, 1507, 1337, 1158 cm^{-1}; MS (ESI/APCI Dual): *m/z* 467 $[M+H]^+$, 465 $[M-H]^-$; Anal. Calcd for $C_{27}H_{31}FN_2O_2S$ HCl: C, 64.46; H, 6.41; N, 5.57. Found: C, 64.33; H, 6.37; N, 5.51.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (22)

Compound **22** was prepared by the same procedure described for **20** using compound **21** instead of compound **19**.

Colorless powder (total yield 50%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.27 (s, 9 H), 3.04–3.16 (m, 3 H), 3.20–3.31 (m, 2 H), 3.34–3.48 (m, 2 H), 3.72–3.82 (m, 1 H), 4.35–4.45 (m, 1 H), 4.63–4.73 (m, 1 H), 7.06–7.15 (m, 4 H), 7.18–7.25 (m, 2 H), 7.33–7.42 (m, 3 H), 7.57–7.68 (m, 2 H), 10.35 (s, 1 H), 11.01 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.9, 28.9, 31.1, 34.2, 48.2, 51.2, 56.1, 115.8, 116.0, 122.7, 122.7, 124.6, 125.4, 126.8, 127.7, 128.4, 133.0, 133.8, 133.9, 138.6, 149.2, 158.2, 159.8; IR (KBr): 2964, 2460, 1507, 1339, 1155 cm^{-1}; MS (ESI/APCI Dual): *m/z* 467 $[M+H]^+$, 465 $[M-H]^-$; Anal. Calcd for $C_{27}H_{31}FN_2O_2S$ HCl: C, 64.46; H, 6.41; N, 5.57. Found: C, 64.31; H, 6.41; N, 5.49.

4-(2-Cyclohexylethoxy)-2-fluoroaniline (24a)

Potassium carbonate (4.15 g, 30.0 mmol) and (2-bromoethyl)cyclohexane (3.76 mL, 24.0 mmol) were added to a solution of 3-fluoro-4-nitrophenol **23** (3.14 g, 20.0 mmol) in DMF (50 mL) at room temperature, and the mixture was stirred overnight. Water was added to the reaction mixture, and the mixture was extracted three times with EtOAc. The organic layer was washed with 1 mol/L hydrochloric acid and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 20% EtOAc/*n*-hexane to afford the target intermediate (2.31 g, 43%) as a pale yellow oil.

To a solution of the above intermediate (2.28 g, 8.52 mmol) in EtOH (25 mL) was added 10% palladium activated carbon (2.28 g) at room temperature, and the mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 20% EtOAc/*n*-hexane to afford **24a** (1.63 g, 81%) as a red oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84–1.05 (m, 2 H), 1.09–1.34 (m, 3 H), 1.40–1.53 (m, 1 H), 1.57–1.81 (m, 7 H), 3.41 (br s, 2 H), 3.90 (t, *J* = 6.7 Hz, 2 H), 6.48–6.76 (m, 3 H); MS (ESI/APCI dual): *m/z* 238 $[M+H]^+$.

Compounds **24b** and **24c** were prepared from the corresponding alkyl halide in the same procedure described for **24a**.

2-Fluoro-4-(hexyloxy)aniline (24b)

Pale yellow oil (yield 55%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82–1.01 (m, 3 H), 1.20–1.52 (m, 6 H), 1.63–1.83 (m, 2 H), 3.42 (br s, 2 H), 3.86 (t, *J* = 6.6 Hz, 2 H), 6.45–6.84 (m, 3 H); MS

(ESI/APCI dual): *m/z* 212 $[M+H]^+$.

2-Fluoro-4-(3-phenylpropoxy)aniline (24c)

Brown oil (yield 64%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95–2.14 (m, 2 H), 2.74–2.83 (m, 2 H), 3.42 (br s, 2 H), 3.87 (t, *J* = 6.3 Hz, 2 H), 6.48–6.77 (m, 3 H), 7.12–7.34 (m, 5 H); MS (ESI/APCI dual): *m/z* 246 $[M+H]^+$.

4-(2-Cyclohexylethoxy)-*N*-(2,4-dimethoxybenzyl)-2-fluoroaniline (25a)

To a solution of **24a** (1.39 g, 5.84 mmol) in THF (20 mL) were added acetic acid (2.01 mL, 35.1 mmol), 2,4-dimethoxybenzaldehyde (1.17 g, 7.01 mmol) and sodium triacetoxyborohydride (3.72 g, 17.6 mmol). The reaction mixture was stirred overnight at room temperature. To the reaction mixture was added 1 mol/L aqueous sodium hydroxide to adjust the pH to 8 to 9, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **25a** (2.28 g, quant.) as a purple oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84–1.06 (m, 2 H), 1.07–1.34 (m, 3 H), 1.36–1.87 (m, 8 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 3.88 (t, *J* = 6.7 Hz, 2 H), 4.01 (br s, 1 H), 4.23 (s, 2 H), 6.34–6.76 (m, 5 H), 7.17 (d, *J* = 8.2 Hz, 1 H).

Compounds **25b** and **25c** were prepared from the corresponding aniline in the same procedure described for **25a**.

***N*-(2,4-Dimethoxybenzyl)-2-fluoro-4-(hexyloxy)aniline (25b)**

Light brown oil (yield 34%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84–0.96 (m, 3 H), 1.26–1.48 (m, 6 H), 1.64–1.81 (m, 2 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.82–3.88 (m, 2 H), 4.01 (br s, 1 H), 4.23 (s, 2 H), 6.32–6.78 (m, 5 H), 7.17 (d, *J* = 8.2 Hz, 1 H).

***N*-(2,4-Dimethoxybenzyl)-2-fluoro-4-(3-phenylpropoxy)aniline (25c)**

Pale yellow oil (yield 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99–2.11 (m, 2 H), 2.73–2.82 (m, 2 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 3.82–3.89 (m, 2 H), 4.03 (br s, 1 H), 4.23 (s, 2 H), 6.38–6.73 (m, 5 H), 7.14–7.22 (m, 4 H), 7.25–7.32 (m, 2 H).

4-[(1*E*)-3-Cyclohexylprop-1-en-1-yl]-2-fluoroaniline (27a)

Toluene (5 mL) was added to 4-bromo-2-fluoroaniline **26** (950 mg, 5.00 mmol), allylcyclohexane (1.15 mL, 7.50 mmol), palladium acetate (112 mg, 0.50 mmol), tris(2-methylphenyl)phosphine (457 mg, 1.50 mmol) and triethylamine (2.09 mL, 15.0 mmol), and the mixture was stirred at reflux temperature for 10 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **27a** (805 mg, 69%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82–1.02 (m, 2 H), 1.03–1.44 (m, 5 H), 1.58–1.80 (m, 4 H), 2.01–2.10 (m, 2 H), 3.67 (br s, 2 H), 5.96–6.07 (m, 1 H), 6.16–6.24 (m, 1 H), 6.65–6.72 (m, 1 H), 6.87–6.93 (m, 1 H), 6.96–7.04 (m, 1 H); MS (ESI/APCI dual): *m/z* 234 $[M+H]^+$.

4-[(1*E*)-3-Cyclopentylprop-1-en-1-yl]-2-fluoroaniline (27b)

1,4-Dioxane (5 mL) and water (1.2 mL) were added to a mixture of 4-bromo-2-fluoroaniline **26** (285 mg, 1.50 mmol), 2-[(1*E*)-3-cyclopentylprop-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (425 mg, 1.80 mmol), tris(dibenzylideneacetone)dipalladium (137 mg, 0.15 mmol), tri-2-furylphosphine (210 mg, 0.90 mmol) and cesium carbonate (976 mg, 3.00 mmol). The mixture was stirred at reflux temperature for 6 h under an argon atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The

resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **27b** (302 mg, 92%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10–1.24 (m, 2 H), 1.44–1.67 (m, 4 H), 1.69–1.82 (m, 2 H), 1.83–2.00 (m, 1 H), 2.12–2.22 (m, 2 H), 3.68 (br s, 2 H), 5.96–6.09 (m, 1 H), 6.17–6.28 (m, 1 H), 6.64–6.74 (m, 1 H), 6.86–6.94 (m, 1 H), 6.96–7.05 (m, 1 H); MS (ESI/APCI dual): *m/z* 220 $[M+H]^+$.

4-(2-Cyclopentylethyl)-2-fluoroaniline (27c)

9-BBN (THF solution, 0.5 mol/L, 33 mL, 16.5 mmol) was added dropwise to a solution of vinylcyclopentane (1.59 g, 16.5 mmol) in THF (7.5 mL) at 0 °C under a nitrogen atomosphere. The mixture was warmed gradually to room temperature and stirred for 15 h. To the reaction mixture were added $PdCl_2$(dppf) (367 mg, 0.45 mmol), 4-bromo-2-fluoroaniline **26** (2.85 g, 15.0 mmol) and 3 mol/L aqueous sodium hydroxide (15 mL, 45.0 mmol), and the mixture was heated at reflux temperature for 10 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% EtOAc/*n*-hexane to afford **27c** (3.01 g, 88%) as a pale yellow oil. To a solution of **27c** (3.01 g) in EtOAc (75 mL) was added 4 mol/L hydrogen chloride in EtOAc (8 mL), and the mixture was stirred at room temperature for 3 h. After the volatiles were removed by rotary evaporation, Et_2O was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **27c** (2.34 g, 64%) as a colorless powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02–1.17 (m, 2 H), 1.40–1.79 (m, 9 H), 2.53–2.60 (m, 2 H), 6.99–7.04 (m, 1 H), 7.11–7.27 (m, 2 H); MS (ESI/APCI dual): *m/z* 208 $[M+H]^+$.

4-[(1*E*)-3-Cyclopropylprop-1-en-1-yl]-2-fluoro-1-nitrobenzene (29)

Iodine (3.05 g, 24.0 mmol) and imidazole (1.63 g, 24.0 mmol) were added to a solution of triphenylphosphine (6.29 g, 24.0 mmol) in $CHCl_3$ (50 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 15 min. A solution of 2-cyclopropylethanol **28** (1.72 g, 20.0 mmol) in $CHCl_3$ (50 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 3 h. To the reaction mixture were added saturated aqueous sodium thiosulfate solution (60 mL) and water (60 mL), and the mixture was extracted with $CHCl_3$. The organic layer was concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 100% *n*-hexane to afford the desired product (2.14 g, 55%) as a pale yellow oil.

Triphenylphosphine (2.86 g, 10.9 mmol) was added to a solution of the above product (2.14 g, 10.9 mmol) in acetonitrile (5 mL), and the mixture was heated at reflux temperature for 15 h. After cooling to room temperature, Et_2O was added to the mixture, and the resulting precipitates were collected by filtration to afford the target intermediate (3.87 g, 77%) as a colorless powder.

To a suspension of the above intermediate (3.83 g, 8.36 mmol) in THF (60 mL) was added dropwise potassium hexamethyldisilazane (toluene solution, 0.5 mol/L, 16.7 mL, 8.36 mmol) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at room temperature for 1 h. After cooling to 0 °C, a solution of 3-fluoro-4-nitrobenzaldehyde (1.23 g, 7.27 mmol) in THF (10 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl was added to the reaction mixture, and the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 25% EtOAc/*n*-hexane to afford **29** (1.42 g, 88%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07–0.21 (m, 2 H), 0.45–0.60 (m, 2 H), 0.74–0.92 (m, 1 H), 2.14–2.30 (m, 2 H), 5.96–6.11 (m, 1 H), 6.36–6.45 (m, 1 H), 7.12–7.31 (m, 2 H), 7.98–8.08 (m,

1 H).

4-(3-Cyclopropylpropyl)-2-fluoroaniline (30)

To a solution of **29** (1.42 g, 6.42 mmol) in EtOH (40 mL) was added 10% palladium activated carbon (150 mg) at room temperature, and the mixture was stirred under a hydrogen atmosphere for 5 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 25% EtOAc/*n*-hexane to afford **30** (709 mg, 57%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.04–0.02 (m, 2 H), 0.36–0.43 (m, 2 H), 0.60–0.73 (m, 1 H), 1.16–1.25 (m, 2 H), 1.60–1.72 (m, 2 H), 2.48–2.55 (m, 2 H), 6.65–6.77 (m, 2 H), 6.78–6.85 (m, 1 H); MS (ESI): *m/z* 194 $[M+H]^+$.

7-Bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonyl chloride (32)

Pyridine (3.79 mL, 47.1 mmol) and DMAP (58.0 mg, 0.471 mmol) were added to a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline **31** (5.00 g, 23.6 mmol) in $CHCl_3$ (80 mL). After cooling to 0 °C, TFAA (3.59 mL, 25.9 mmol) was added in a dropwise manner to the mixture. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with EtOAc. The mixture was washed with 1 mol/L hydrochloric acid, saturated aqueous $NaHCO_3$ and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 25% EtOAc/*n*-hexane to afford the intermediate (6.97 g, 96%) as a pale yellow oil.

Chlorosulfonic acid (20.0 mL, 301 mmol) was added in a dropwise manner to a solution of the above intermediate (4.95 g, 16.1 mmol) in $CHCl_3$ (15 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h and at 60 °C for 2 h. After cooling to room temperature, the reaction

mixture was added in a dropwise manner to ice water, and the mixture was extracted four times with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 34% EtOAc/*n*-hexane, and the fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added Et_2O, and the resulting precipitates were collected by filtration to afford **32** (3.14 g, 48%) as a colorless powder. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 10% to 34% EtOAc/*n*-hexane, and the fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added Et_2O, and the resulting precipitates were collected by filtration to afford **32** (1.56 g, 24%) (Total 4.70 g, 72%) as a colorless powder: mp 103–105 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.97–3.08 (m, 2 H), 3.87–4.00 (m, 2 H), 4.79–4.91 (m, 2 H), 7.62–7.69 (m, 1 H), 7.99–8.05 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.4, 28.8, 40.9, 42.7, 44.8, 46.3, 115.2, 117.2, 118.3, 131.0, 131.3, 133.8, 133.9, 134.3, 134.7, 140.0, 140.5, 141.6; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{11}H_8BrClF_3NO_3S$ $[M-H]^-$, 403.8976. Found: 403.8994.

***N*-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33a)**

Pyridine (3.09 mL, 38.4 mmol) was added to a solution of 4-fluoroaniline (3.73 g, 33.6 mmol) in $CHCl_3$ (107 mL). After cooling to 0 °C, **32** (13.0 g, 32.0 mmol) was added to the mixture. The mixture was warmed to room temperature and stirred for 13 h. To the mixture was added 1 mol/L hydrochloric acid, and the mixture was extracted with $CHCl_3$. The organic layer was concentrated under reduced pressure, and to the residue was added 20% EtOAc/*n*-hexane. The resulting precipitates were collected by filtration to afford crude product (14.5 g, 94%) as an orange powder.

To a solution of the above product (14.5 g, 30.2 mmol) in MeOH (200 mL) and EtOAc (100

mL) was added 10% palladium activated carbon (4.36 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 15 h. Then to the mixture was added 10% palladium activated carbon (2.00 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. EtOH was added to the residue, and the resulting precipitates were collected by filtration to afford the intermediate (10.6 g, 88%) as a colorless powder.

An aqueous solution (10 mL) of potassium hydroxide (2.24 g, 40.0 mmol) was added to a suspension of the above intermediate (8.05 g, 20.0 mmol) in EtOH (40 mL), and the mixture was stirred at room temperature for 15 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with water. After cooling to 0 °C, 3 mol/L hydrochloric acid was added dropwise to adjust the pH to 7 to 8. The resulting precipitates were collected by filtration to afford **33a** (6.04 g, 99%) as a colorless powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.65–2.72 (m, 2 H), 2.87–2.94 (m, 2 H), 3.84 (s, 2 H), 7.05–7.10 (m, 4 H), 7.16 (d, J = 8.1 Hz, 1 H), 7.38–7.45 (m, 2 H); MS (ESI/APCI dual): *m/z* 307 $[M+H]^+$.

Compounds **33b** to **33h** were prepared from the corresponding aniline in the same procedure described for **33a**.

***N*-[4-(2-Cyclohexylethoxy)-2-fluorophenyl]-*N*-(2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-isoquinoline-6-sulfonamide (33b)**

Colorless amorphous (yield 68%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89–1.00 (m, 2 H), 1.11–1.30 (m, 4 H), 1.40–1.50 (m, 1 H), 1.54–1.77 (m, 6 H), 2.79–2.86 (m, 2 H), 3.15–3.17 (m, 2 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.85–3.95 (m, 2 H), 4.08 (s, 2 H), 4.67 (s, 2 H), 6.25–6.29 (m, 1 H), 6.35–6.40 (m, 1 H), 6.45–6.52 (m, 2 H), 6.87–6.93 (m, 1 H), 7.07–7.12 (m, 1 H), 7.19–7.25 (m, 1 H), 7.46–7.50 (m, 2 H); MS (ESI): *m/z* 583 $[M+H]^+$.

***N*-(2,4-Dimethoxybenzyl)-*N*-[2-fluoro-4-(hexyloxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33c)**

Pale yellow oil (yield 81%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–0.94 (m, 3 H), 1.24–1.50 (m, 4 H), 1.63–1.81 (m, 4 H), 2.82 (t, *J* = 5.8 Hz, 2 H), 3.16 (t, *J* = 5.8 Hz, 2 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.86 (t, *J* = 6.5 Hz, 2 H), 4.08 (s, 2 H), 4.67 (s, 2 H), 6.27 (d, *J* = 2.3 Hz, 1 H), 6.37 (dd, *J* = 8.2, 2.3 Hz, 1 H), 6.43–6.52 (m, 2 H), 6.84–6.94 (m, 1 H), 7.08–7.13 (m, 1 H), 7.20–7.27 (m, 1 H), 7.44–7.52 (m, 2 H); MS (ESI/APCI dual): *m/z* 557 $[M+H]^+$.

***N*-(2,4-Dimethoxybenzyl)-*N*-[2-fluoro-4-(3-phenylpropoxy)phenyl]-1,2,3,4-tetrahydro-isoquinoline-6-sulfonamide (33d)**

Colorless amorphous (yield 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97–2.16 (m, 2 H), 2.71–2.86 (m, 4 H), 3.11–3.20 (m, 2 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.83–3.89 (m, 2 H), 4.08 (s, 2 H), 4.67 (s, 2 H), 6.26–6.28 (m, 1 H), 6.35–6.40 (m, 1 H), 6.43–6.51 (m, 2 H), 6.86–6.94 (m, 1 H), 7.06–7.34 (m, 7 H), 7.44–7.52 (m, 2 H); MS (ESI/APCI dual): *m/z* 591 $[M+H]^+$.

***N*-[4-(3-Cyclohexylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33e)**

Colorless powder (yield 66%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.73–0.88 (m, 2 H), 1.01–1.26 (m, 6 H), 1.42–1.73 (m, 7 H), 2.42–2.51 (m, 2 H), 2.65–2.75 (m, 2 H), 2.90–3.00 (m, 2 H), 3.89 (s, 2 H), 6.86–7.02 (m, 2 H), 7.05–7.20 (m, 2 H), 7.34–7.46 (m, 2 H); MS (ESI/APCI dual): *m/z* 431 $[M+H]^+$.

***N*-[4-(3-Cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33f)**

Colorless powder (yield 61%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93–1.09 (m, 2 H), 1.17–

1.29 (m, 2 H), 1.40–1.60 (m, 6 H), 1.63–1.78 (m, 3 H), 2.40–2.53 (m, 2 H), 2.65–2.75 (m, 2 H), 2.90–2.97 (m, 2 H), 3.88 (s, 2 H), 6.87–6.99 (m, 2 H), 7.05–7.19 (m, 2 H), 7.37–7.44 (m, 2 H); MS (ESI/APCI dual): *m/z* 417 $[M+H]^+$.

***N*-[4-(3-Cyclopropylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33g)**

Colorless powder (yield 91%): ^{1}H NMR (300 MHz, DMSO-d_6): δ -0.07–0.01 (m, 2 H), 0.33–0.40 (m, 2 H), 0.59–0.72 (m, 1 H), 1.09–1.19 (m, 2 H), 1.54–1.66 (m, 2 H), 2.48–2.57 (m, 2 H), 2.81–2.89 (m, 2 H), 3.12–3.20 (m, 2 H), 4.10 (s, 2 H), 6.91–7.03 (m, 2 H), 7.08–7.16 (m, 1 H), 7.26–7.32 (m, 1 H), 7.46–7.52 (m, 2 H); MS (ESI/APCI dual): *m/z* 389 $[M+H]^+$.

***N*-[4-(2-Cyclopentylethyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33h)**

Colorless powder (yield 94%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99–1.16 (m, 2 H), 1.37–1.79 (m, 9 H), 2.45–2.56 (m, 2 H), 2.80–2.89 (m, 2 H), 3.09–3.20 (m, 2 H), 4.10 (s, 2 H), 6.90–7.03 (m, 2 H), 7.06–7.16 (m, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.45–7.53 (m, 2 H); MS (ESI/APCI dual): *m/z* 403 $[M+H]^+$.

2-[(4-*tert*-Butylphenyl)acetyl]-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (34a)

To a suspension of **33a** (153 mg, 0.500 mmol) in $CHCl_3$ (10 mL) were added (4-*tert*-butylphenyl)acetic acid (106 mg, 0.650 mmol), HOBt・H_2O (100 mg, 0.650 mmol) and EDC・HCl (125 mg, 0.650 mmol). The reaction mixture was stirred at room temperature for 15 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The

resulting residue was purified using a silica gel column eluted with 25% to 60% EtOAc/*n*-hexane. The fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added EtOAc/IPE/*n*-hexane, and the resulting precipitates were collected by filtration to afford **34a** (142 mg, 59%) as a colorless powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9 H), 2.73–2.83 (m, 2 H), 3.62–3.76 (m, 4 H), 4.62–4.78 (m, 2 H), 7.04–7.19 (m, 6 H), 7.24–7.39 (m, 3 H), 7.47–7.56 (m, 2 H), 10.20 (br s, 1 H); MS (ESI/APCI dual): *m/z* 481 $[M+H]^+$.

2-[(4-*tert*-Butylphenyl)acetyl]-*N*-[4-(2-cyclohexylethoxy)-2-fluorophenyl]-1,2,3,4-tetra-hydroisoquinoline-6-sulfonamide (34b)

To a suspension of **33b** (468 mg, 0.803 mmol) in DMF (10 mL) were added (4-*tert*-butylphenyl)acetic acid (132 mg, 0.879 mmol), HOBt・H_2O (207 mg, 1.04 mmol) and EDC・HCl (199 mg, 1.04 mmol). The reaction mixture was stirred at room temperature for 19 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 30% to 50% EtOAc/*n*-hexane to afford the intermediate (530 mg, 80%) as a colorless powder.

To a solution of the above intermediate (500 mg, 0.661 mmol) in $CHCl_3$ (1.8 mL) was added TFA (1.77 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and EtOAc/*n*-hexane was added to the residue. The resulting precipitate was collected by filtration to afford **34b** (270 mg, 67%) as a colorless powder: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80–1.02 (m, 2 H), 1.09–1.27 (m, 2 H), 1.26 (s, 9 H), 1.34–1.46 (m, 1 H), 1.49–1.78 (m, 8 H), 2.74–2.84 (m, 2 H), 3.64–3.81 (m, 4 H), 3.88–3.99 (m, 2 H), 4.64–4.81 (m, 2 H), 6.65–6.81 (m, 2 H), 6.97–7.08 (m, 1 H), 7.11–7.20 (m, 2 H),

7.24–7.41 (m, 3 H), 7.43–7.51 (m, 2 H), 9.77 (s, 1 H); MS (ESI): *m/z* 607 $[M+H]^+$.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (22)

A borane-THF complex (0.9 mol/L THF solution, 0.550 mL, 0.500 mmol) was added to a solution of **34a** (120 mg, 0.250 mmol) in THF (10 mL) at 0 °C, and the mixture was heated at reflux temperature for 5 h. After cooling to room temperature, 6 mol/L hydrochloric acid (6 mL) was added, and the mixture was stirred at reflux temperature for 3 h. The mixture was cooled to 0 °C, 6 mol/L aqueous sodium hydroxide was added to adjust the pH to 8 to 9, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with $CHCl_3$ to 5% MeOH/$CHCl_3$ to afford **22** (115 mg, 99%) as a colorless amorphous. To a solution of **22** in EtOAc (4 mL) was added 4 mol/L hydrogen chloride in EtOAc (1 mL), and the mixture was stirred at room temperature for 15 h. After the volatiles were removed by rotary evaporation, EtOAc/Et_2O was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **22** (115 mg, 92%) as a colorless powder.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(2-cyclohexylethoxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (35)

Compound **35** was prepared by the same procedure described for **22** using **34b** instead of **34a**.

Colorless powder (yield 45%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.88–0.98 (m, 2 H), 1.08–1.34 (m, 4 H), 1.27 (s, 9 H), 1.36–1.46 (m, 1 H), 1.52–1.74 (m, 7 H), 3.04–3.17 (m, 3 H), 3.18–3.50 (m, 3 H), 3.75–3.84 (m, 1 H), 3.87–4.01 (m, 2 H), 4.38–4.49 (m, 1 H), 4.67–4.78 (m, 1 H), 6.66–6.74 (m, 1 H), 6.75–6.82 (m, 1 H), 7.02–7.09 (m, 1 H), 7.18–7.28 (m, 2 H), 7.32–7.44 (m,

3 H), 7.52–7.64 (m, 2 H), 9.90 (br s, 1 H), 10.79 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 24.9, 25.7, 26.0, 29.0, 31.1, 32.6, 33.9, 34.2, 35.9, 48.4, 51.3, 56.1, 66.2, 102.4, 102.6, 110.7, 115.9, 116.0, 124.7, 125.4, 126.7, 127.5, 128.4, 129.2, 132.7, 139.5, 149.2, 156.4, 158.2, 158.3; IR (KBr): 2925, 2563, 1512, 1342, 1157 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{35}H_{45}FN_2O_3S$ $[M+H]^+$, 593.3208. Found: 593.3208.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[2-fluoro-4-(hexyloxy)phenyl]-1,2,3,4-tetrahydroiso-quinoline-6-sulfonamide (36)

i) To a solution of **33c** (520 mg, 0.935 mmol) in 1,2-dichloroethane (3 mL) were added a solution of (4-*tert*-butylphenyl)acetaldehyde (181 mg, 1.03 mmol) in 1,2-dichloroethane (2 mL) and sodium triacetoxyborohydride (297 mg, 1.40 mmol), and the mixture was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 20% to 34% EtOAc/*n*-hexane to afford the intermediate (622 mg, 93%) as a pale yellow oil.

ii) To a solution of the above intermediate (593 mg, 0.827 mmol) in $CHCl_3$ (5 mL) was added anisole (5 mL), the mixture was cooled to 0 °C. To the mixture was added TFA (1 mL), and the mixture was stirred at room temperature for 21 h. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a NH silica gel column eluted with 50% to 100% EtOAc/*n*-hexane to afford **36** (378 mg, 76%) as a pale yellow amorphous.

iii) To a solution of **36** in EtOAc (5 mL) was added 4 mol/L hydrogen chloride in EtOAc (1 mL), and the mixture was stirred overnight at room temperature. To the reaction mixture was

added *n*-hexane, and the mixture was stirred for 1 h. The resulting precipitates were collected by filtration to afford the monohydrochloride salt of **36** (376 mg, 92%) as a colorless powder: ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.80–0.92 (m, 3 H), 1.25–1.30 (m, 4 H), 1.27 (s, 9 H), 1.33–1.42 (m, 2 H), 1.62–1.70 (m, 2 H), 3.02–3.28 (m, 4 H), 3.34–3.50 (m, 3 H), 3.76–3.85 (m, 1 H), 3.91 (t, *J* = 6.4 Hz, 2 H), 4.40–4.52 (m, 1 H), 4.68–4.79 (m, 1 H), 6.67–6.72 (m, 1 H), 6.75–6.79 (m, 1 H), 7.03–7.10 (m, 1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 7.35–7.43 (m, 3 H), 7.55–7.62 (m, 2 H), 9.90 (s, 1 H), 10.46 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 13.9, 22.0, 24.9, 25.1, 28.4, 28.9, 30.9, 31.1, 34.2, 48.3, 51.2, 56.1, 68.1, 102.4, 102.5, 110.7, 116.0, 116.1, 124.6, 125.4, 126.7, 127.5, 128.4, 129.2, 132.7, 133.5, 133.9, 139.5, 149.2, 156.6, 158.2, 158.3; IR (KBr): 2956, 2570, 1513, 1344, 1156 cm^{-1}; MS (ESI): *m/z* 607 $[M+H]^+$; Anal. Calcd for $C_{33}H_{43}FN_2O_3S$ HCl: C, 65.71; H, 7.35; N, 4.64. Found: C, 65.53; H, 7.29; N, 4.53.

Compound **37** was prepared from the corresponding **33d** in the same procedure described for **36**. Compounds **38** to **41** were prepared from the corresponding **33e** to **33h** in the same procedure described for **36-(i)** and **(iii)**.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[2-fluoro-4-(3-phenylpropoxy)phenyl]-1,2,3,4-tetra-hydroisoquinoline-6-sulfonamide (37)

Colorless powder (yield 63%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.27 (s, 9 H), 1.94–2.02 (m, 2 H), 2.68–2.73 (m, 2 H), 3.02–3.24 (m, 4 H), 3.35–3.51 (m, 3 H), 3.76–3.84 (m, 1 H), 3.89–3.96 (m, 2 H), 4.41–4.52 (m, 1 H), 4.69–4.79 (m, 1 H), 6.68–6.82 (m, 2 H), 7.03–7.12 (m, 1 H), 7.15–7.31 (m, 7 H), 7.35–7.43 (m, 3 H), 7.55–7.64 (m, 2 H), 9.91 (s, 1 H), 10.28 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.9, 31.1, 30.2, 31.3, 34.2, 48.3, 51.2, 56.1, 67.4, 102.5, 102.6, 110.7, 116.1, 116.2, 124.6, 125.4, 125.9, 126.7, 127.5, 128.3, 128.4, 129.2, 132.7, 133.5, 133.9, 139.5, 141.2, 149.2, 156.6, 158.2, 158.2; IR (KBr): 2955, 2570, 1513, 1343, 1155 cm^{-1}; MS (ESI): *m/z* 601 $[M+H]^+$; Anal. Calcd for $C_{36}H_{41}FN_2O_3S$ HCl: C, 67.85; H, 6.64; N, 4.40.

Found: C, 67.83; H, 6.63; N, 4.32.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(3-cyclohexylpropyl)-2-fluorophenyl]-1,2,3,4-tetra-hydroisoquinoline-6-sulfonamide (38)

Colorless powder (yield 56%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77–0.86 (m, 2 H), 1.05–1.23 (m, 6 H), 1.27 (s, 9 H), 1.48–1.54 (m, 2 H), 1.56–1.68 (m, 5 H), 2.44–2.53 (m, 2 H), 3.04–3.17 (m, 3 H), 3.19–3.48 (m, 4 H), 3.75–3.83 (m, 1 H), 4.40–4.48 (m, 1 H), 4.68–4.75 (m, 1 H), 6.92–6.96 (m, 1 H), 6.97–7.02 (m, 1 H), 7.10–7.14 (m, 1 H), 7.20–7.25 (m, 2 H), 7.34–7.43 (m, 3 H), 7.57–7.65 (m, 2 H), 10.10 (s, 1 H), 10.60 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.9, 25.8, 26.2, 27.8, 28.9, 31.1, 32.8, 34.2, 34.6, 36.4, 36.8, 48.2, 51.2, 56.1, 115.6, 115.7, 121.4, 121.5, 124.4, 124.6, 125.4, 126.6, 126.8, 127.6, 128.4, 132.8, 133.6, 133.9, 139.5, 142.7, 142.7, 149.2, 154.9, 156.6; IR (KBr): 2924, 2566, 1512, 1332, 1154 cm^{-1}; MS (ESI/APCI dual): *m/z* 591 $[M+H]^+$, 589 $[M-H]^-$; Anal. Calcd for $C_{36}H_{47}FN_2O_2S$ HCl: C, 68.93; H, 7.71; N, 4.47. Found: C, 68.83; H, 7.66; N, 4.42.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetra-hydroisoquinoline-6-sulfonamide (39)

Colorless powder (yield 60%): mp 195–197 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.94–1.06 (m, 2 H), 1.20–1.29 (m, 2 H), 1.27 (s, 9 H), 1.41–1.59 (m, 6 H), 1.66–1.76 (m, 3 H), 2.49–2.54 (m, 2 H), 3.06–3.19 (m, 3 H), 3.28–3.45 (m, 4 H), 3.73–3.81 (m, 1 H), 4.39–4.48 (m, 1 H), 4.66–4.75 (m, 1 H), 6.92–6.97 (m, 1 H), 6.98–7.03 (m, 1 H), 7.08–7.13 (m, 1 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.34–7.42 (m, 3 H), 7.57–7.65 (m, 2 H), 10.12 (s, 1 H), 11.64 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.7, 24.8, 28.9, 29.7, 31.1, 32.2, 34.1, 34.6, 35.1, 48.2, 51.2, 56.1, 115.6, 115.7, 121.4, 121.5, 124.4, 124.5, 125.4, 126.6, 126.8, 127.5, 128.4, 132.8, 133.6, 133.9, 139.5, 142.7, 142.7, 149.2, 154.9, 156.6; IR (KBr): 2951, 2560, 1514, 1346, 1159 cm^{-1};

MS (ESI/APCI dual): *m/z* 577 $(M+H)^+$, 575 $(M-H)^-$; Anal. Calcd for $C_{35}H_{45}FN_2O_2S$ HCl: C, 68.55; H, 7.56; N, 4.57. Found: C, 68.46; H, 7.57; N, 4.55; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{35}H_{45}FN_2O_2S$ $[M+H]^+$, 577.3259. Found: 577.3248.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(3-cyclopropylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (40)

Colorless powder (yield 84%): ^{1}H NMR (600 MHz, DMSO-d_6): δ -0.05–0.02 (m, 2 H), 0.33–0.40 (m, 2 H), 0.62–0.70 (m, 1 H), 1.11–1.18 (m, 2 H), 1.27 (s, 9 H), 1.56–1.64 (m, 2 H), 2.44–2.57 (m, 2 H), 3.02–3.49 (m, 7 H), 3.75–3.84 (m, 1 H), 4.40–4.49 (m, 1 H), 4.68–4.76 (m, 1 H), 6.92–7.03 (m, 2 H), 7.10–7.16 (m, 1 H), 7.19–7.26 (m, 2 H), 7.35–7.43 (m, 3 H), 7.56–7.66 (m, 2 H), 10.11 (s, 1 H), 10.62 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 4.3, 10.4, 24.9, 29.0, 30.6, 31.1, 33.5, 34.1, 34.2, 48.4, 51.3, 56.1, 115.6, 115.7, 121.4, 121.5, 124.4, 124.6, 125.4, 126.6, 126.8, 127.6, 128.4, 132.8, 133.8, 139.5, 142.6, 142.7, 149.2, 154.8, 156.7; IR (KBr): 2962, 2572, 1513, 1333, 1155 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{33}H_{41}FN_2O_2S$ $[M+H]^+$, 549.2946. Found: 549.2935.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(2-cyclopentylethyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (41)

Colorless powder (yield 72%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.04–1.12 (m, 2 H), 1.27 (s, 9 H), 1.41–1.60 (m, 6 H), 1.63–1.74 (m, 3 H), 2.45–2.55 (m, 2 H), 3.05–3.16 (m, 3 H), 3.20–3.46 (m, 4 H), 3.74–3.83 (m, 1 H), 4.40–4.48 (m, 1 H), 4.66–4.76 (m, 1 H), 6.93–6.97 (m, 1 H), 6.98–7.03 (m, 1 H), 7.09–7.15 (m, 1 H), 7.20–7.24 (m, 2 H), 7.35–7.42 (m, 3 H), 7.57–7.64 (m, 2 H), 10.10 (s, 1 H), 10.82 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 24.7, 24.9, 31.1, 32.1, 33.6, 34.2, 37.1, 48.4, 51.3, 56.1, 115.6, 115.7, 121.4, 121.5, 124.4, 124.6, 125.4, 126.6, 126.8, 127.6, 128.4, 132.8, 133.6, 133.9, 139.5, 142.8, 142.9, 149.2, 154.8, 156.7; IR (KBr): 2953,

2565, 1513, 1335, 1155 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{34}H_{43}FN_2O_2S$ $[M+H]^+$, 563.3102. Found: 563.3089.

_N_-(2,4-Dimethoxybenzyl)-_N_-(2-fluoro-4-hydroxyphenyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (42)

Pyridine (2.22 mL, 27.4 mmol) was added to a solution of **9** (3.80 g, 13.7 mmol) in $CHCl_3$ (50 mL), and **32** (5.07 g, 12.5 mmol) was added to the mixture. The mixture was stirred at room temperature for 5 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 30% to 50% EtOAc/*n*-hexane to afford the target intermediate (6.52 g, 81%) as a colorless amorphous.

To a solution of the above intermediate (6.50 g, 10.0 mmol) in MeOH (50 mL) and EtOAc (50 mL) was added triethylamine (1.68 mL, 12.1 mmol) and 10% palladium activated carbon (650 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 2% to 50% EtOAc/*n*-hexane to afford **42** (4.94 g, 87%) as a colorless amorphous: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90–3.10 (m, 2 H), 3.54 (s, 3 H), 3.69 (s, 3 H), 3.80–3.91 (m, 2 H), 4.54 (s, 2 H), 4.83–4.93 (m, 2 H), 6.37–6.53 (m, 4 H), 6.75–6.80 (m, 1 H), 7.04–7.13 (m, 1 H), 7.43–7.63 (m, 3 H), 10.05 (br s, 1 H); MS (ESI/APCI dual): *m/z* 591 $[M+Na]^+$.

2-[2-(4-*tert*-Butylphenyl)ethyl]-_N_-(2,4-dimethoxybenzyl)-_N_-[2-fluoro-4-(pentyloxy)-phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (43a)

To a solution of **42** (400 mg, 0.704 mmol) in DMF (1 mL) were added 1-iodopentane (119 μL, 0.915 mmol) and potassium carbonate (146 mg, 1.06 mmol), and the mixture was stirred at room temperature overnight. To the reaction mixture was added saturated aqueous $NaHCO_3$,

and the mixture was extracted with EtOAc. The organic layer was filtered through a phase separator and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 15% to 30% EtOAc/*n*-hexane to afford the target intermediate (307 mg, 68%) as a colorless amorphous.

An aqueous solution (0.5 mL) of potassium hydroxide (59 mg, 1.06 mmol) was added to a solution of the above intermediate (307 mg, 0.48 mmol) in EtOH (3 mL), and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was diluted with water. The mixture was extracted with EtOAc, and the organic layer was filtered through a phase separator, concentrated under reduced pressure to afford the crude product (252 mg) as a colorless amorphous.

To a solution of the above product (125 mg, 0.23 mmol) in $CHCl_3$ (1 mL) were added a solution of (4-*tert*-butylphenyl)acetaldehyde (50.0 mg, 0.28 mmol) in $CHCl_3$ (1 mL) and sodium triacetoxyborohydride (146 mg, 0.69 mmol), and the mixture was stirred at room temperature for 19 h. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the mixture was extracted with $CHCl_3$. The organic layer was filtered through a phase separator and concentrated under reduced pressure to afford **43a** (162 mg, quant.) as a colorless amorphous: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88–0.94 (m, 3 H), 1.31 (s, 9 H), 1.32–1.42 (m, 4 H), 1.69–1.77 (m, 2 H), 2.76–2.86 (m, 4 H), 2.86–2.92 (m, 2 H), 2.92–2.97 (m, 2 H), 3.56 (s, 3 H), 3.74 (s, 3 H), 3.76 (s, 2 H), 3.84 (t, *J* = 6.6 Hz, 2 H), 4.65 (s, 2 H), 6.24–6.27 (m, 1 H), 6.34–6.39 (m, 1 H), 6.42–6.49 (m, 2 H), 6.83–6.88 (m, 1 H), 7.09–7.14 (m, 1 H), 7.15–7.23 (m, 3 H), 7.29–7.37 (m, 2 H), 7.43–7.52 (m, 2 H); MS (ESI/APCI dual): *m/z* 703 $[M+H]^+$.

Compounds **43b** and **43c** were prepared from **42** using 1-iodoheptane and 1-iodooctane, respectively, in the same procedure described for **43a**.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(2,4-dimethoxybenzyl)-*N*-[2-fluoro-4-(heptyloxy)-

phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (43b)

Colorless amorphous (total yield 36%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83–0.95 (m, 3 H), 1.18–1.44 (m, 8 H), 1.32 (s, 9 H), 1.67–1.80 (m, 2 H), 2.76–3.02 (m, 8 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.78 (s, 2 H), 3.81–3.89 (m, 2 H), 4.67 (s, 2 H), 6.25–6.29 (m, 1 H), 6.34–6.41 (m, 1 H), 6.43–6.53 (m, 2 H), 6.84–6.93 (m, 1 H), 7.08–7.25 (m, 4 H), 7.31–7.39 (m, 2 H), 7.44–7.55 (m, 2 H); MS (ESI): *m/z* 731 $[M+H]^+$.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-(2,4-dimethoxybenzyl)-*N*-[2-fluoro-4-(octyloxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (43c)

Colorless amorphous (total yield 42%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85–0.91 (m, 3 H), 1.23–1.35 (m, 8 H), 1.31 (s, 9 H), 1.36–1.43 (m, 2 H), 1.69–1.75 (m, 2 H), 2.76–2.99 (m, 8 H), 3.56 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 2 H), 3.82–3.86 (m, 2 H), 4.66 (s, 2 H), 6.24–6.28 (m, 1 H), 6.33–6.39 (m, 1 H), 6.43–6.51 (m, 2 H), 6.82–6.91 (m, 1 H), 7.10–7.14 (m, 1 H), 7.16–7.23 (m, 3 H), 7.31–7.36 (m, 2 H), 7.44–7.53 (m, 2 H); MS (ESI): *m/z* 745 $[M+H]^+$.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[2-fluoro-4-(pentyloxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (44a)

To a solution of **43a** (162 mg, 0.230 mmol) in $CHCl_3$ (4 mL) was added TFA (880 μL), and the mixture was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was washed with brine, filtered through a phase separator, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 30% to 70% EtOAc/*n*-hexane to afford **44a** (20 mg, 16%) as a colorless amorphous.

To a solution of **44a** (20 mg, 0.036 mmol) in EtOAc (0.5 mL) was added 4 mol/L hydrogen chloride in EtOAc (90 μL), and the mixture was stirred at room temperature for 5 min. After the

volatiles were removed by rotary evaporation, EtOAc was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **44a** (3.0 mg, 14%) as a colorless powder: ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.84–0.92 (m, 3 H), 1.27 (s, 9 H), 1.29–1.38 (m, 4 H), 1.64–1.70 (m, 2 H), 3.02–3.50 (m, 7 H), 3.76–3.84 (m, 1 H), 3.91 (t, *J* = 6.4 Hz, 2 H), 4.41–4.48 (m, 1 H), 4.68–4.77 (m, 1 H), 6.67–6.73 (m, 1 H), 6.75–6.81 (m, 1 H), 7.02–7.09 (m, 1 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 7.35–7.44 (m, 3 H), 7.54–7.61 (m, 2 H), 9.91 (s, 1 H), 10.79 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 13.9, 21.8, 24.9, 27.6, 28.2, 31.1, 34.2, 48.3, 51.2, 56.1, 68.1, 102.4, 102.5, 110.7, 116.0, 116.1, 124.6, 125.4, 126.7, 127.5, 128.4, 129.2, 132.7, 133.5, 133.9, 139.5, 149.2, 156.6, 158.3, 158.3; IR (KBr): 2958, 2570, 1512, 1343, 1155 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{32}H_{41}FN_2O_3S$ $[M+H]^+$, 553.2895. Found: 553.2883.

Compounds **44b** and **44c** were prepared from **43b** and **43c**, respectively, in the same procedure described for **44a**.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[2-fluoro-4-(heptyloxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (44b)

Colorless amorphous (total yield 29%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.83–0.89 (m, 3 H), 1.24–1.32 (m, 6 H), 1.27 (s, 9 H), 1.33–1.40 (m, 2 H), 1.63–1.70 (m, 2 H), 3.04–3.49 (m, 7 H), 3.77–3.85 (m, 1 H), 3.88–3.94 (m, 2 H), 4.40–4.51 (m, 1 H), 4.66–4.78 (m, 1 H), 6.66–6.81 (m, 2 H), 7.02–7.10 (m, 1 H), 7.19–7.27 (m, 2 H), 7.33–7.45 (m, 3 H), 7.52–7.63 (m, 2 H), 9.90 (s, 1 H), 10.67 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.0, 22.0, 24.9, 25.4, 28.4, 28.5, 29.0, 31.1, 31.2, 34.2, 48.4, 51.3, 56.1, 68.1, 102.4, 102.6, 110.7, 115.9, 116.1, 124.7, 125.4, 126.7, 127.6, 128.4, 129.2, 132.7, 133.9, 139.5, 149.3, 156.4, 158.3, 158.3; IR (KBr): 2956, 2570, 1513, 1343, 1156 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{34}H_{45}FN_2O_3S$ $[M+H]^+$, 581.3208. Found: 581.3204.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[2-fluoro-4-(octyloxy)phenyl]-1,2,3,4-tetrahydroiso-quinoline-6-sulfonamide (44c)

Colorless amorphous (total yield 33%): ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.81–0.90 (m, 3 H), 1.22–1.32 (m, 8 H), 1.27 (s, 9 H), 1.34–1.39 (m, 2 H), 1.62–1.70 (m, 2 H), 3.00–3.48 (m, 7 H), 3.76–3.85 (m, 1 H), 3.88–3.93 (m, 2 H), 4.40–4.51 (m, 1 H), 4.67–4.78 (m, 1 H), 6.66–6.82 (m, 2 H), 7.01–7.09 (m, 1 H), 7.20–7.25 (m, 2 H), 7.34–7.44 (m, 3 H), 7.53–7.64 (m, 2 H), 9.90 (s, 1 H), 10.80 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.0, 22.1, 24.9, 25.4, 28.5, 28.6, 28.7, 29.0, 31.1, 31.2, 34.2, 48.4, 51.4, 56.1, 68.1, 102.4, 102.5, 110.7, 115.9, 116.1, 124.7, 125.4, 126.7, 127.6, 128.4, 129.2, 132.7, 133.8, 139.5, 149.3, 156.4, 158.3, 158.3; IR (KBr): 2956, 2570, 1513, 1343, 1156 cm^{-1}; HRMS (ESI/APCI Dual): *m/z* Calcd for $C_{35}H_{47}FN_2O_3S$ $[M+H]^+$, 595.3364. Found 595.3346.

4-(3-Cyclopentylpropyl)-2-fluoroaniline (45)

9-BBN (THF solution, 0.5 mol/L, 1.81 L, 907 mmol) was added in a dropwise manner to a solution of allylcyclopentane **52** (100 g, 907 mmol) in THF (400 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed gradually to room temperature and stirred overnight. After the reaction mixture was cooled to 0 °C, $PdCl_2$(dppf) (20.2 g, 24.8 mmol), 4-bromo-2-fluoroaniline **26** (157 g, 825 mmol) and 3 mol/L aqueous sodium hydroxide (827 mL, 2.48 mol) were added to the reaction mixture, and the mixture was heated at the reflux temperature for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, and the resulting residue was diluted with EtOAc. The mixture was washed with water, and the aqueous layer was filtered through a pad of Celite® and extracted with EtOAc. The combined organic layers were washed with brine, and the aqueous layer was filtered through a pad of Celite® and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 10% to 24% EtOAc/*n*-hexane. The fractions incruding product were collected and evaporated by rotary evaporation, and to the residue was added 50% EtOAc/*n*-hexane and NH silica gel (150 g). The mixture was stirred at room temperature for 0.5 h, filtered, and concentrated under reduced pressure to afford crude **45** (201 g) as an orange oil.

To a solution of **45** (201 g) in EtOAc (1.5 L) was added 4 mol/L hydrogen chloride in EtOAc (309 mL), and the mixture was stirred overnight at room temperature. After the volatiles were removed by rotary evaporation, EtOAc (500 mL) was added to the residue, and the resulting precipitates were collected by filtration to afford the monohydrochloride salt of **45** (137 g, 64%) as a colorless powder: mp 118–120 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.97–1.09 (m, 2 H), 1.23–1.32 (m, 2 H), 1.41–1.61 (m, 6 H), 1.66–1.79 (m, 3 H), 2.58 (t, J = 7.6 Hz, 2 H), 7.06–7.11

(m, 1 H), 7.20–7.25 (m, 1 H), 7.41–7.48 (m, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.7, 29.8, 32.2, 34.6, 35.0, 115.9, 116.0, 118.8, 118.9, 124.1, 124.9, 143.6, 153.9, 155.6; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{14}H_{20}FN$ $[M+H]^+$, 222.1653. Found: 222.1653.

***N*-[4-(3-Cyclopentylpropyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (46)**

Pyridine (49.5 μL, 0.615 mmol) and DMAP (3.75 mg, 0.0307 mmol) were added to a solution of 4-(3-cyclopentylpropyl)-2-fluoroaniline hydrochloride **45** (83.2 mg, 0.323 mmol) in $CHCl_3$ (3 mL) at room temperature. The mixture was cooled to 0 °C, and **18** (101 mg, 0.307 mmol) was added to the mixture. The reaction mixture was warmed to room temperature and stirred for 19 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The mixture was washed with 1 mol/L hydrochloric acid, and then with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 20% EtOAc/*n*-hexane to afford **46** (150 mg, 95%) as a colorless amorphous: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98–1.09 (m, 2 H), 1.25–1.32 (m, 2 H), 1.45–1.61 (m, 6 H), 1.69–1.77 (m, 3 H), 2.52 (t, *J* = 7.8 Hz, 2 H), 2.91–2.98 (m, 2 H), 3.81–3.91 (m, 2 H), 4.74–4.84 (m, 2 H), 6.63–6.69 (m, 1 H), 6.76–6.82 (m, 1 H), 6.89–6.95 (m, 1 H), 7.16–7.23 (m, 1 H), 7.42–7.49 (m, 1 H), 7.55–7.64 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.2, 21.0, 25.1, 27.7, 29.1, 30.2, 32.6, 35.5, 35.6, 39.9, 41.2, 42.9, 45.4, 46.7, 115.2, 115.3, 121.3, 121.4, 124.1, 124.2, 124.7, 125.5, 125.5, 126.8, 127.3, 127.5, 127.7, 134.4, 135.2, 136.6, 137.0, 137.9, 138.4, 142.7, 153.5, 153.6, 155.2, 155.9; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{25}H_{28}F_4N_2O_3S$ $[M+H]^+$, 513.1830. Found: 513.1821.

***N*-[4-(3-Cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide**

(33f)

An aqueous solution (2 mL) of potassium hydroxide (88.0 mg, 1.56 mmol) was added to a suspension of **46** (401 mg, 0.782 mmol) in EtOH (8 mL), and the mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with water. After cooling to 0 °C, the resulting mixture was acidified by the addition of 1 mol/L hydrochloric acid, and saturated aqueous $NaHCO_3$ was added to adjust the pH to 7 to 8. The resulting precipitates were collected by filtration to afford **33f** (313 mg, 96%) as a colorless powder: mp 176–178 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.96–1.05 (m, 2 H), 1.20–1.27 (m, 2 H), 1.41–1.58 (m, 6 H), 1.65–1.76 (m, 3 H), 2.44–2.51 (m, 2 H), 2.69 (t, *J* = 5.9 Hz, 2 H), 2.94 (t, *J* = 5.9 Hz, 2 H), 3.88 (s, 2 H), 6.87–6.91 (m, 1 H), 6.93–6.98 (m, 1 H), 7.09 (t, *J* = 8.3 Hz, 1 H), 7.14–7.18 (m, 1 H), 7.37–7.44 (m, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 24.7, 28.3, 29.7, 32.2, 34.5, 35.0, 42.6, 47.4, 115.4, 115.5, 123.5, 124.2, 126.0, 126.8, 127.0, 135.8, 138.1, 141.0, 141.4, 154.7, 156.3; MS (ESI/APCI dual): *m/z* 417 $[M+H]^+$; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{23}H_{29}FN_2O_2S$ $[M+H]^+$, 417.2007. Found: 417.1993.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (39)

To a solution of **33f** (100 mg, 0.240 mmol) in THF (8 mL) were added a solution of (4-*tert*-butylphenyl)acetaldehyde (47.0 mg, 0.264 mmol) in THF (2 mL), and the mixture was stirred at room temperature for 5 min. To the mixture was added sodium triacetoxyborohydride (76.0 mg, 0.360 mmol), and the mixture was stirred at room temperature for 15 h. Saturated aqueous $NaHCO_3$ and water were added to the reaction mixture, and the mixture was extracted 3 times with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 30% EtOAc/*n*-hexane to afford **39** (96.0 mg, 69%) as a colorless

gum.

To a solution of **39** in EtOAc (5 mL) was added 4 mol/L hydrogen chloride in EtOAc (1 mL), and the mixture was stirred at room temperature for 15 h. After the volatiles were removed by rotary evaporation, 20% EtOAc/*n*-hexane was added to the residue. The resulting precipitates were collected by filtration to afford the monohydrochloride salt of **39** (89.0 mg, 87%) as a colorless powder.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (47)

Pyridine (3.79 mL, 47.1 mmol) and DMAP (58.0 mg, 0.471 mmol) were added to a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline **31** (5.00 g, 23.6 mmol) in $CHCl_3$ (80 mL). After cooling to 0 °C, TFAA (3.59 mL, 25.9 mmol) was added in a dropwise manner to the mixture. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with EtOAc. The mixture was washed with 1 mol/L hydrochloric acid, saturated aqueous $NaHCO_3$ and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 25% EtOAc/*n*-hexane to afford **47** (6.97 g, 96%) as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.86–2.96 (m, 2 H), 3.80–3.90 (m, 2 H), 4.69–4.79 (m, 2 H), 7.01–7.08 (m, 1 H), 7.24–7.38 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.3, 28.8, 41.6, 43.1, 45.0, 46.5, 115.4, 117.3, 120.3, 120.4, 128.9, 129.4, 129.9, 130.2, 130.5, 130.6, 132.2, 133.5, 155.8, 156.1; HRMS (EI): *m/z* Calcd for $C_{11}H_9BrF_3NO$ $[M]^+$, 306.9820. Found: 306.9792.

7-Bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonyl chloride (32)

Chlorosulfonic acid (20.0 mL, 301 mmol) was added in a dropwise manner to a solution of **47** (4.95 g, 16.1 mmol) in $CHCl_3$ (15 mL) at 0 °C, and the mixture was stirred at room temperature

for 1 h and at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was added in a dropwise manner to ice water, and the mixture was extracted four times with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 34% EtOAc/*n*-hexane, and the fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added Et_2O, and the resulting precipitates were collected by filtration to afford **32** (3.14 g, 48%) as a colorless powder. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 10% to 34% EtOAc/*n*-hexane, and the fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added Et_2O, and the resulting precipitates were collected by filtration to afford **32** (1.56 g, 24%) (Total 4.70 g, 72%) as a colorless powder.

7-Bromo-*N*-(4-fluorophenyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfon-amide (48)

To a solution of **32** (2.67 g, 6.57 mmol) in $CHCl_3$ (20 mL) was added 4-fluoroaniline (0.690 mL, 7.22 mmol), pyridine (1.06 mL, 13.1 mmol) and DMAP (80.0 mg, 0.657 mmol) at room temperature. The mixture was stirred for 3 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with EtOAc. The mixture was washed with 1 mol/L hydrochloric acid, saturated aqueous $NaHCO_3$ and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 10% to 40% EtOAc/*n*-hexane, and the fractions incruding product were collected and evaporated by rotary evaporation. To the residue was added 14% EtOAc/*n*-hexane, and the resulting precipitates were collected by filtration to afford **48** (2.94 g, 93%) as a colorless powder: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.83–2.92 (m, 2 H), 3.79–3.91 (m, 2 H), 4.69–4.83 (m, 2 H), 6.88–6.98 (m, 2 H), 7.09–7.19 (m, 2 H), 7.47–7.54 (m, 1 H), 7.74–

7.83 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.2, 28.6, 41.0, 42.7, 44.7, 46.1, 116.3, 116.4, 117.2, 117.3, 124.7, 124.8, 124.9, 125.0, 131.3, 132.5, 132.7, 133.0, 133.6, 138.4, 160.1, 161.8; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{17}H_{13}BrF_4N_2O_3S$ $[M+H]^+$, 480.9839. Found: 480.9836.

***N*-(4-Fluorophenyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (21)**

To a solution of **48** (900 mg, 1.87 mmol) in EtOH (15 mL) and EtOAc (15 mL) was added 10% palladium activated carbon (450 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 15 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 40% to 50% EtOAc/*n*-hexane to afford **21** (738 mg, 98%) as a colorless powder: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.92–2.98 (m, 2 H), 3.82–3.92 (m, 2 H), 4.75–4.85 (m, 2 H), 6.63 (br s, 1 H), 6.93–6.99 (m, 2 H), 7.01–7.08 (m, 2 H), 7.17–7.25 (m, 1 H), 7.53–7.59 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.8, 29.2, 41.2, 42.9, 45.4, 116.2, 116.4, 124.8, 124.9, 125.0, 125.6, 126.9, 127.5, 127.6, 127.8, 131.9, 134.5; MS (ESI/APCI dual): *m/z* 403 $[M+H]^+$; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{17}H_{14}F_4N_2O_3S$ $[M+H]^+$, 403.0734. Found: 403.0731.

Debromination using hydrogenolysis; General procedure

To a solution of 7-bromo-1,2,3,4-tetrahydroisoquinolne derivatives (0.312 mmol) in EtOH (2.5 mL) and EtOAc (2.5 mL) was added 10% palladium activated carbon (10 wt%) and triethylamine (52.1 μL, 0.374 mmol). The mixture was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified using a silica gel column to afford the desired product.

***N*-[4-(3-Cyclohexylpropyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (49)**

Colorless powder (yield quant.): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76–0.91 (m, 2 H), 1.07–1.24 (m, 6 H), 1.51–1.59 (m, 2 H), 1.60–1.74 (m, 5 H), 2.47–2.53 (m, 2 H), 2.91–2.99 (m, 2 H), 3.81–3.92 (m, 2 H), 4.73–4.85 (m, 2 H), 6.72 (br s, 1 H), 6.76–6.81 (m, 1 H), 6.89–6.94 (m, 1 H), 7.16–7.23 (m, 1 H), 7.42–7.48 (m, 1 H), 7.56–7.53 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.1, 26.3, 26.6, 27.7, 28.3, 33.3, 35.5, 36.9, 37.4, 41.2, 42.9, 45.3, 60.4, 115.2, 115.3, 117.3, 121.3, 121.4, 124.1, 124.2, 124.7, 125.4, 125.5, 126.8, 127.3, 127.5, 127.7, 134.7, 135.2, 136.6, 136.9, 137.8, 138.3, 142.6, 142.6, 142.7, 153.6, 155.2, 155.9, 156.1; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{26}H_{30}F_4N_2O_3S$ $[M+H]^+$, 527.1986. Found: 527.1975.

***N*-[4-(2-Cyclopentylethyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (50)**

Colorless powder (yield 98%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03–1.16 (m, 2 H), 1.43–1.80 (m, 9 H), 2.50–2.59 (m, 2 H), 2.90–3.01 (m, 2 H), 3.80–3.92 (m, 2 H), 4.74–4.84 (m, 2 H), 6.65 (br s, 1 H), 6.76–6.83 (m, 1 H), 6.89–6.96 (m, 1 H), 7.14–7.25 (m, 1 H), 7.42–7.49 (m, 1 H), 7.55–7.64 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 25.2, 27.7, 29.1, 32.6, 34.5, 37.6, 39.5, 41.2, 42.9, 45.4, 46.8, 115.1, 115.3, 124.2, 124.7, 125.5, 126.9, 127.3, 127.5, 127.7, 134.4, 137.0, 137.8, 142.8; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{24}H_{26}F_4N_2O_3S$ $[M+H]^+$, 499.1673. Found: 499.1665.

***N*-[4-(2-Cyclopropylethyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (51)**

Colorless powder (yield 97%): ^{1}H NMR (600 MHz, $CDCl_3$): δ -0.04–0.00 (m, 2 H), 0.37–0.43

(m, 2 H), 0.59–0.68 (m, 1 H), 1.42–1.49 (m, 2 H), 2.61–2.69 (m, 2 H), 2.90–3.01 (m, 2 H), 3.81–3.96 (m, 2 H), 4.73–4.89 (m, 2 H), 6.70–6.76 (m, 1 H), 6.78–6.85 (m, 1 H), 6.91–6.98 (m, 1 H), 7.17–7.25 (m, 1 H), 7.43–7.50 (m, 1 H), 7.56–7.64 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 27.7, 29.1, 30.6, 31.3, 35.3, 36.2, 41.2, 42.9, 45.4, 46.8, 115.3, 115.4, 121.3, 124.1, 124.2, 124.8, 125.5, 126.8, 127.3, 127.5, 127.7, 134.4, 135.2, 136.9, 137.8, 153.5, 155.1; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{22}H_{22}F_4N_2O_3S$ $[M+H]^+$, 471.1360. Found: 471.1353.

Synthesis of compound 1 on a 100 gram-scale

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (47)

Pyridine (41.7 mL, 519 mmol) and DMAP (576 mg, 4.72 mmol) were added to a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline **31** (100 g, 472 mmol) in $CHCl_3$ (600 mL). After cooling to 0 °C, TFAA (66.5 mL, 481 mmol) was added in a dropwise manner to the mixture. The mixture was warmed to room temperature and stirred for 15 h, then concentrated under reduced pressure. To the resulting residue was added 1 mol/L hydrochloric acid, and the mixture was extracted with EtOAc. The organic layer was washed with 1 mol/L hydrochloric acid and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was diluted with $CHCl_3$, and the mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **47** (143 g, 98%) as a pale yellow oil.

7-Bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonyl chloride (32)

Chlorosulfonic acid (180 mL, 2.71 mol) was added in a dropwise manner to a solution of **47** (139 g, 452 mmol) in $CHCl_3$ (180 mL) at room temperature, and the mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the reaction mixture was added in a dropwise manner to ice water. $CHCl_3$ (1.5 L) and water (500 mL) were added to the mixture, and the

mixture was stirred at 40 °C. The mixture was separated, and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined, washed with water, and concentrated under reduced pressure. To the residue was added EtOAc (89 mL) and IPE (520 mL), and the mixture was stirred at room temperature for 20 h. The resulting precipitates were collected by filtration to afford **32** (98.9 g, 54%) as a pale yellow powder. The filtrate was concentrated under reduced pressure, and EtOAc (40 mL) and *n*-hexane (120 mL) was added to the resulting residue. The mixture was then stirred at room temperature for 20 h. The resulting precipitates were collected by filtration to afford **32** (11.2 g, 6%) as a pale yellow powder (total: 110 g, 60%).

7-Bromo-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetra-hydroisoquinoline-6-sulfonamide (53)

Pyridine (36.2 mL, 450 mmol) was added to a solution of **45** (47.3 g, 184 mmol) in $CHCl_3$ (450 mL) at 0 °C. A solution of **32** (73.2 g, 180 mmol) in $CHCl_3$ (150 mL) was added to the mixture, and the mixture was warmed to room temperature and stirred for 4 h. To the mixture was added 1 mol/L hydrochloric acid (200 mL) and 3 mol/L hydrochloric acid (150 mL) at 0 °C, and the mixture was extracted twice with $CHCl_3$. The aqueous layer was extracted with EtOAc, and the organic layers were combined and concentrated under reduced pressure to afford crude **53** (119 g) as an orange powder: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98–1.08 (m, 2 H), 1.24–1.31 (m, 2 H), 1.44–1.60 (m, 6 H), 1.67–1.76 (m, 3 H), 2.50 (t, *J* = 7.6 Hz, 2 H), 2.87–2.93 (m, 2 H), 3.80–3.90 (m, 2 H), 4.72–4.82 (m, 2 H), 6.79–6.89 (m, 2 H), 7.25 (s, 1 H), 7.34–7.40 (m, 1 H), 7.48–7.53 (m, 1 H), 7.81–7.87 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.2, 21.0, 25.1, 27.3, 28.6, 30.1, 32.6, 35.5, 35.6, 39.9, 41.0, 42.8, 44.7, 46.1, 60.4, 115.3, 115.4, 115.5, 117.2, 117.8, 121.0, 123.4, 123.6, 124.6, 132.1, 132.3, 132.6, 133.1, 133.2, 133.9, 137.0, 137.4, 137.8, 138.3, 142.5, 153.5, 155.1; HRMS (ESI/APCI dual): *m/z* Calcd for $C_{25}H_{27}BrF_4N_2O_3S$ $[M+H]^+$, 591.0935. Found: 591.0927.

***N*-[4-(3-Cyclopentylpropyl)-2-fluorophenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (46)**

To a solution of **53** (118 g) in EtOH (400 mL) and EtOAc (100 mL) was added 10% palladium activated carbon (12.0 g) and triethylamine (27.6 mL, 198 mmol). The mixture was then stirred under a hydrogen atmosphere at room temperature for 1 h. Celite® was added to the mixture, and the mixture was filtered and concentrated under reduced pressure. The resulting residue was diluted with $CHCl_3$, and to the mixture was added 1 mol/L hydrochloric acid (600 mL) at 0 °C. The mixture was extracted with $CHCl_3$ (twice) and EtOAc. The organic layers were combined and concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with 20% to 50% EtOAc/*n*-hexane to afford **46** (89.4 g, 97% in 2 steps) as a pale yellow gum.

***N*-[4-(3-Cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (33f)**

An aqueous solution (100 mL) of potassium hydroxide (11.7 g, 209 mmol) was added to a suspension of **46** (89.4 g, 174 mmol) in EtOH (400 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h. The mixture was concentrated under reduced pressure, and the resulting residue was diluted with water (500 mL). The mixture was neutralized with an aqueous solution of $KHSO_4$ (49.67 g, 365 mmol), and the resulting precipitates were collected by filtration to afford **33f** (78.3 g, quant.) as a colorless powder.

2-[2-(4-*tert*-Butylphenyl)ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide (39)

To a solution of **33f** (78.3 g, 174 mmol) in $CHCl_3$ (500 mL) were added a solution of

(4-*tert*-butylphenyl)acetaldehyde (33.8 g, 192 mmol) in $CHCl_3$ (100 mL) and sodium triacetoxyborohydride (55.4 g, 262 mmol), and the mixture was stirred at room temperature for 4 h. To the mixture were added (4-*tert*-butylphenyl)acetaldehyde (6.61 g, 37.5 mmol) and sodium triacetoxyborohydride (18.5 g, 87.2 mmol), and the mixture was stirred at room temperature for 18 h. Saturated aqueous $NaHCO_3$ (1 L) was added to the reaction mixture, and the mixture was extracted three times with $CHCl_3$. The organic layer was concentrated under reduced pressure, and the resulting residue was purified using a silica gel column eluted with 30% to 50% EtOAc/*n*-hexane to afford **39** (88.1 g, 88%) as a pale yellow amorphous.

To a solution of **39** in EtOAc (400 mL) was added 4 mol/L hydrogen chloride in EtOAc (57.3 mL), and the mixture was stirred at room temperature for 20 h. After the volatiles were removed by rotary evaporation, EtOAc was added to the residue, and the mixture was stirred at 0 °C. The resulting precipitates were collected by filtration to afford the monohydrochloride salt of **39** (84.5 g, 90%) as a colorless powder.

薬理試験、in vitro 肝代謝安定性試験および物性試験に関する実験

in vitro 薬理試験

MGAT2 阻害試験

This assay detects CoA, a product of the MGAT2-catalyzed deacylation of oleoyl-CoA. The free thiol of CoA can react with 7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin (CPM), a pro-fluorescent coumarin maleimide derivative that becomes fluorescent upon reaction with thiols.

In this assay, recombinant human and mouse MGAT2 were produced in the baculovirus expression system. The MGAT2 activity was determined as follows: Assay buffer [final concentration: 100 mM Tris-HCl (pH 7.5), 100 mM sucrose, 5 mM $MgCl_2$] and recombinant MGAT2 and test compound were added to each well of a 96-well black plate (Corning). Substrate solution [final concentration: 5.3 μM oleoyl-CoA, 0.78 μM 2-oleoylglycerol, 7.5 μM phosphatidylcholine] were added to start the reaction, which was allowed to proceed for 20 min. The reaction was terminated upon the addition of CPM with final concentration 5 μM. The plates were sealed, incubated for 20 min. Fluorescence that emits at 460 nm when excited at 380 nm was counted on a SpectraMax Plate Reader (Molecular Devices, LLC). Oleoyl-CoA, 2-oleoylglycerol and phosphatidylcholine were obtained from Sigma-Aldrich and CPM from Life Technologies.

in vivo 薬理試験

脂肪負荷吸収抑制試験

C57BL/6J male mice (10 weeks old, n = 7 to 8) were used. To inhibit the clearance of plasma triacylglycerol, we administered 100 μl of the surfactant tyloxapol (10% in PBS) through a tail vein. Immediately, we administered orally 4 mL/kg of test compound or 0.5% MC solution as

vehicle. After 30 min, we had challenged orally with 4.4 mL/kg of triolein containing 0.1 mCi/mL 3*H* triolein. We collected blood from tail vein at 2 h, 3 h and 4 h after lipid challenge and counted scintillation. Efficacy was calculated as the percentage reduction in area under the curve of plasma scintillation for 4 h ($AUC_{0\text{-}4h}$) compared to vehicle-treated control animals. Bartlett's test was applied to evaluate the equality of variance for $AUC_{0\text{-}4h}$ between vehicle and treated mice. If the equality of variance isn't statistically significant in Bartlett's test, Dunnett's test is applied to establish statistical significance of $AUC_{0\text{-}4h}$ between vehicle and treated mice. If the equality of variance is statistically significant in Bartlett's test, Steel's test is applied to establish statistical significance of $AUC_{0\text{-}4h}$ between vehicle and treated mice. Student's t-test was used to establish statistical significance in the comparison between 2 groups.

in vitro 肝代謝安定性試験

Test substances (5 μM) were incubated at 37 ˚C in 1 mg/mL human or mouse microsomes supplemented with 1.5 mM glucose-6-phosphate, 0.16 mM ß-nicotinamide-adenine dinucleotide phosphate, 0.18 units/mL glucose-6-phosphate dehydrogenase, 2.4 mM magnesium chloride and 69 mM potassium chloride in 250 mM phosphate buffer (pH 7.4). Concentrations of the test compounds were determined by LC-MS/MS. The %metabolized was determined by comparing a peak area of the test substance at 15 min incubation with the peak area at 0 min.

溶解度測定試験

An excess amount of each compound was added to Water and shaken on a shaker (model SR-2s; Yamato Kagaku) at 25 °C for 24 h.

An excess amount of each compound was added to FeSSIF (pH 5.0) and shaken on a shaker (model SR-2s; Yamato Kagaku) at 25 °C for 2 h and keep on 37 °C for 22 h on a water bath (model LT-10s; Yamato Kagaku).

The suspensions were centrifuged at 3000 and 11000 rpm for 10 min, and supernatant was diluted with 50% aqueous acetonitrile or 50% aqueous MeOH solution. The concentrations were measured by HPLC. The HPLC analysis was performed using a Shimadzu HPLC system composed of a LC-20AD, SPD-20A and SIL-20AC. The conditions for HPLC were as follows: mobile phase, 0.1% Phosphoric acid aqueous solution/acetonitrile; flow rate, 0.8 mL/min.; column, reversed-phase (Shimpack XR-ODS, 2.2 μm, 2.0 x 75 mm; Shimadzu) at 40 °C; and detection wavelength, 210 nm.

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